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

Updates effective November 01, 2025

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 ArrayRx 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 ArrayRx 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 ArrayRx 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.pdf**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP108

Split Fill Management*

Description

Acalabrutinib (Calquence) and its active metabolite inhibit Bruton tyrosine kinase (BTK) by irreversibly bonding to the active BTK site. This prevents activation of the signaling proteins CD86 and CD69, as well as inhibits proliferation and survival of malignant B cells.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
acalabrutinib (Calquence)	100 mg capsule	Mantle cell lymphoma (previously treated); Chronic lymphocytic leukemia (CLL); small lymphocytic lymphoma (SLL)	60 capsules/30 days
	100 mg tablets		60 tablets/30 days

Initial Evaluation

I. **Acalabrutinib (Calquence)** 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. Member has <u>not</u> experienced disease progression while on a BTK inhibitor [e.g. zanubrutinib (Brukinsa®), ibrutinib (Imbruvica®)]; **AND**
   D. A diagnosis of one of the following:
      1. **Chronic Lymphocytic Leukemia (CLL) or small lymphocytic lymphoma (SLL)**; **AND**
         i. Medication is used in **<u>one</u>** of the following settings:
            a. Previously untreated CLL/SLL; **AND**
               i. Medication will be used as monotherapy or in combination with obinutuzumab (Gazyva); **OR**
            b. Relapsed or refractory after at least <u>one</u> prior systemic therapy; **AND**
               i. Member has **<u>not</u>** experienced disease progression while on venetoclax (Vencelxta) or a phosphoinositide-3 kinase inhibitor [e.g. duvelisib (Copiktra), idelalisib (Zydelig)]; **AND**

ii. Medication will **not** be used in combination with other oncologic medications (i.e., will be used as monotherapy)

II. Acalabrutinib (Calquence) is considered investigational when used for all other conditions, including but not limited to:
   A. Mantle cell lymphoma (MCL)
   B. Diffuse Large B-Cell Lymphoma
   C. Head and neck squamous cell carcinoma
   D. Ovarian cancer
   E. Non-small cell lung cancer (NSCLC)
   F. Severe Chronic Graft Versus Host Disease
   G. Waldenström's macroglobulinemia (WM)

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. Medication will **not** be used in combination with other oncologic medications (i.e., will be used as monotherapy); **OR**
   A. Acalabrutinib (Calquence) will be used in combination with obinutuzumab (Gazyva) in the setting of previously untreated CLL/SLL; **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., no signs of disease progression).

Supporting Evidence

I. Safety and efficacy of acalabrutinib (Calquence) has not been established in the pediatric population.
II. CLL and SLL are difficult, life threatening diseases, accordingly treatment with acalabrutinib (Calquence) requires consultation with an oncologist or hematologist.
III. There is no published data from a head-to-head studies between acalabrutinib (Calquence) and other BTK inhibitors [zanubrutinib (Brukinsa), ibrutinib (Imbruvica)] to show superiority of one BTK inhibitor over another. There is also no published data in the use of BTK inhibitors in patients diagnosed with MCL or CLL/SLL that have relapsed or are refractory to other BTK inhibitors. Additionally, no data is available to show one BTK inhibitor could overcome common mechanisms of resistance of BTK inhibitors.
IV. The efficacy of acalabrutinib (Calquence) in patients with CLL was demonstrated in two randomized, controlled trials which included patients with SLL because it is the same disease. In the ELEVATE-TN trial, a randomized, multicenter, open-label, actively controlled, three-arm trial of acalabrutinib (Calquence) in combination with obinutuzumab, acalabrutinib (Calquence) monotherapy, and obinutuzumab in combination with chlorambucil in patients with previously untreated chronic lymphocytic leukemia, both the acalabrutinib (Calquence) monotherapy arm

and acalabrutinib (Calquence) in combination with obinutuzumab arm significantly prolonged progression free survival (PFS) when compared to obinutuzumab plus chlorambucil.

V. The efficacy of acalabrutinib (Calquence) in patients with relapsed or refractory CLL was based on a multicenter, randomized, open-label trial (ASCEND). The trial enrolled patients with relapsed or refractory CLL after at least one prior systemic therapy, while excluding those with transformed disease, prolymphocytic leukemia, or who had previous treatment with venetoclax, a Bruton tyrosine kinase inhibitor, or a phosphoinositide-3 kinase inhibitor. Interim analysis results indicate acalabrutinib (Calquence) significantly prolonged PFS when compared to rituximab combined with idelalisib or bendamustine.

Investigational or Not Medically Necessary Uses

I. Acalabrutinib (Calquence) has not been sufficiently evaluated outside CLL/SLL. Limited evidence is available consisting of early phase studies evaluating use in other cancers; however, safety and efficacy have not been established in these conditions:
   A. Mantle cell lymphoma (MCL)
      i. For the treatment of MCL, acalabrutinib (Calquence) 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.
      ii. Acalabrutinib (Calquence) was studied in an open-label, phase 2 study in 124 patients with relapsed or refractory mantle cell lymphoma. Oral acalabrutinib (100 mg twice per day) was given until disease progression or unacceptable toxicity. At a median follow-up of 15.2 months, 100 (81%) patients achieved an overall response. The most common prior therapies in clinical trials included rituximab, bendamustine + rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) - based regimen, Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), bortezomib or carfilzomib, stem-cell transplant and lenalidomide.
      iii. Treatment of MCL with acalabrutinib (Calquence) 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.
   B. Diffuse Large B-Cell Lymphoma
   C. Head and neck squamous cell carcinoma
   D. Ovarian cancer
   E. Non-small cell lung cancer (NSCLC)
   F. Severe Chronic Graft Versus Host Disease
   G. Waldenström's macroglobulinemia (WM)

** 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. Calquence [Prescribing Information]. Wilmington, DE: AstraZeneca; November 2019.
2. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391(10121):659-667.
3. ClinicalTrials.gov. Elevate CLL TN: Study of Obinutuzumab + Chlorambucil, Acalabrutinib (ACP-196) + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL. NCT02475681
4. ClinicalTrials.gov. A Study of Acalabrutinib vs Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in R/R CLL. NCT02970318.
5. AstraZeneca (2019). ELEVATE-TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab or Alone vs Obinutuzumab plus Chlorambucil in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia [PowerPoint slides]. Retrieved from AstraZeneca.
6. AstraZeneca (2019). Acalabrutinib vs Rituximab plus Idelalisib or Bendamustine by Investigator's Choice in Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from a Pre-Planed Interim Analysis of Phase 3 Ascend Study [PowerPoint slides]. Retrieved from AstraZeneca.

Policy Implementation/Update:

Action and Summary of Changes	Date
Revised renewal criteria for clarity	02/2025
Added 100mg tablet formulation to the policy	08/2022
Removed initial criteria and moved MCL indication to investigational or not medically necessary uses section	01/2022
Updated criteria to policy format. Addition of age requirement to ages 18 and older. Require member has not experienced disease progression while on a BTK inhibitor. Added new indication of CLL/SLL.	12/2019
Previous Reviews	02/2018
Criteria created	01/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP002

Split Fill Management* (applies to ensartinib [Ensacove], lorlatinib [Lorbrena], crizotinib [Xalkori], ceritinib [Zykadia] and brigatinib [Alunbrig] only)

Description

Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), lorlatinib (Lorbrena), and ensartinib (Ensacove) are orally administered anaplastic lymphoma kinase positive (ALK+) tyrosine kinase inhibitors (TKI).

Length of Authorization

- Initial: Six months
- Renewal: 12 months
    i. Up to a maximum duration of 2 years for alectinib (Alecensa) for adjuvant treatment of NSCLC

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
crizotinib (Xalkori)	ALK+ NSCLC, metastatic; ROS1+ NSCLC, metastatic; ALK+ IMT, unresectable, recurrent, refractory	200 mg capsules	60 capsules/30 days
		250 mg capsules	60 capsules/30 days
	ALK+ systemic ALCL, relapsed/refractory; ALK+ IMT, unresectable, recurrent, refractory	200 mg capsules	120 capsules/30 days
		250 mg capsules	120 capsules/30 days
alectinib (Alecensa)	ALK+ NSCLC, adjuvant treatment, metastatic	150 mg capsules	240 capsules/30 days
ceritinib (Zykadia)	ALK+ NSCLC, metastatic	150 mg capsules	84 capsules/28 days
		150 mg tablets	84 tablets/28 days
brigatinib (Alunbrig)		30 mg tablets	180 tablets/30 days
		90 mg tablets	30 tablets/30 days
		90 mg and 180 mg tablet titration pack	30 tablets/30 days
		180 mg tablets	30 tablets/30 days
lorlatinib (Lorbrena)		25 mg tablets	90 tablets/30 days
		100 mg tablets	30 tablets/30 days
ensartinib (Ensacove)		25 mg capsule	90 capsules/30 days
		100 mg capsule	60 capsules/30 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Initial Evaluation

I. **Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), lorlatinib (Lorbrena), and ensartinib (Ensacove)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. The medication will not be used in combination with other agents and will be used as monotherapy for the diagnosis submitted; **AND**
   C. A diagnosis of **Non-Small Cell Lung Cancer (NCSLC); AND**
   D. Meets one of the following:
      1. Request is for the **adjuvant treatment** following complete tumor resection; **AND**
         i. Member has completely resected stage II–IIIA or stage IIIB (T3, N2) NSCLC or tumors are ≥ 4 cm or node positive; **AND**
         ii. Disease is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test; **OR**
      2. Member has **recurrent, advanced or metastatic (stage IV)** disease; **AND**
         i. Disease is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test; **AND**
            a. The request is for alectinib (Alecensa), ceritinib (Zykadia), or brigatinib (Alunbrig); **AND**
               i. The member has not progressed on any other agent listed in this policy; **OR**
               ii. The member has progressed on or after use of crizotinib (Xalkori); **OR**
            b. The request is for crizotinib (Xalkori) or ensartinib (Ensacove); **AND**
               i. The member has not progressed on any other agent listed in this policy; **OR**
            c. The request is for lorlatinib (Lorbrena); **OR**
         ii. **Disease is ROS1+ as detected by an FDA-approved test**; **AND**
            a. The request is for crizotinib (Xalkori) or ceritinib (Zykadia)

II. Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), lorlatinib (Lorbrena), and ensartinib (Ensacove) are considered investigational when used for all other conditions, including but not limited to:
   A. ALK+ systemic Anaplastic Large Cell Lymphoma (ALCL) in patients one year of age and older
   B. Inflammatory myofibroblastic tumors (IMT)
   C. NSCLC outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
   D. Erdheim-Chester Disease (ECD) with ALK fusion
   E. Large B-Cell Lymphoma (LBCL)
   F. NSCLC in combination with other therapies
   G. Thyroid cancer
   H. Melanoma
   I. Gastrointestinal cancer
   J. Prostate cancer
   K. Leukemias or lymphomas
   L. Urothelial 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. Medication will not be used in combination with another targeted chemotherapy (e.g. Alectinib (Alecensa), brigatinb (Alunbrig), ceritinib (Zykadia), crizotinib (Xalcori)); **AND**
IV. There is documentation of disease response with treatment, defined by stabilization of disease, decrease in tumor size, or tumor spread.

Supporting Evidence

I. There is currently no evidence for safety and efficacy of any of these agents in combination with another ALK inhibitor, or in combination with any other therapies for the treatment of non-small-cell lung cancer (NSCLC). Any open prior authorizations for other ALK-inhibitors will be closed if coverage is approved for an agent in this policy. These agents have only been studied for the adjuvant treatment, metastatic, and adult populations with NSCLC in clinical trials.
II. The National Comprehensive Cancer Network guidelines for treatment of ALK-positive NSCLC (version 3.2025) recommend alectinib (Alecensa), brigatinib (Alunbrig), lorlatinib (Lobrena), and ensartinib (Ensacove) as first line treatment (category 1, preferred) and crizotinib (Xalkori) and ceritinib (Zykadia) as useful in certain circumstances (category 1).

Alectinib (Alecensa)

III. Alectinib (Alecensa) is indicated as adjuvant treatment in adult patients following tumor resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumors ≥ 4 cm or node positive), as detected by an FDA-approved test. Alectinib (Alecensa) was evaluated in the international, open-label, phase 3 ALINA trial which assessed the efficacy and safety of 24 months of adjuvant alectinib vs. platinum-based chemotherapy in 257 patients with completely resected stage IB to IIIA ALK-positive NSCLC. The primary endpoint was disease-free survival (DFS). Patients were randomized to receive oral alectinib (600 mg twice daily) for 24 months or chemotherapy (cisplatin and vinorelbine, gemcitabine, or pemetrexed) for four 21-day cycles. Treatment with alectinib reduced the risk of recurrence or death by 76% (HR, 0.24; 95% CI, 0.13–0.45; P<0.001) compared with adjuvant chemotherapy alone. The alectinib group also had a 78% improvement in central nervous system DFS (HR, 0.22; 95% CI, 0.08–0.58). Alectinib was well tolerated with no new safety signals. Therapy with alectinib (Alecensa) for two years is recommended as a category 1 treatment for patients with completely resected stage and positive for ALK rearrangements.
IV. Alectinib (Alecensa) has been evaluated in the first-line setting for metastatic ALK+ NSCLC, or after progression on crizotinib (Xalkori). A class review was done in 2018 which revealed advantages with alectinib (Alecensa) including superior head-to-head progression-free survival (PFS), intracranial response compared to crizotinib, and a more favorable safety profile via indirect comparison. As of September 2024, NCCN guideline for NSCLC list the following as first line therapy for ALK-positive NSCLC when ALK rearrangement is discovered prior to first line systemic therapy (all category 1): alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena) are preferred, ceritinib (Zykadia) is marked as “other recommended treatment,” and crizotinib ((Xalkori) marked useful in certain circumstances for performance status 0-4.

V. A review of clinical data indicates that all ALK+ tyrosine kinase inhibitors indicated in the first-line treatment setting have comparable evidence with no agent standing out as superior to others (based on efficacy analysis supported by improvement in PFS, comparable toxicity profiles, and no clear survival advantage reported for any of the agents). Alectinib was recommended as the preferred first-line therapy of ALK-positive NSCLC by National Comprehensive Cancer Network (NCCN) NSCLC panel (V9.2024) (based on clinical trial data from ALEX and J-ALEX trials). As of September 2024, this recommendation remains unchanged. Additionally, alectinib (Alecensa) has been evaluated after progression on crizotinib (Xalkori) or lorlatinib (Lorbrena); however, safety and efficacy after progression on ceritinib (Zykadia) and/or brigatinib (Alunbrig) are unknown.

VI. Patients typically have disease progression after first-line therapy with alectinib, brigatinib, ceritinib, crizotinib, or lorlatinib; subsequent therapy recommendations are described in the algorithm and often include continuing the first-line targeted therapies, depending on the type of progression. In the second line setting, several agents have been evaluated after progression on crizotinib (Xalkori). Lorlatinib (Lorbrena) is the only agent at this time that has been evaluated in the third line setting following progression on crizotinib (Xalkori) and one other ALK+ TKI for NSCLC.

Lorlatinib (Lobrena)

VII. Lorlatinib (Lorbrena) received its FDA-approval for second or greater line therapy in the metastatic setting of NSCLC. In March 2021, lorlatinib (Lorbrena) received expanded approval in the first line setting for metastatic ALK+ NSCLC based on the data from a phase 3, open-label, randomized clinical trial (CROWN study). In 296 previously untreated patients with advanced metastatic ALK+ NSCLC, lorlatinib (Lorbrena) showed higher efficacy as compared to crizotinib (Xalkori) based on a 12-month PFS rate of 78% (95% CI; 70, 84) versus that of 39% (95% CI, 30 to 48) in crizotinib arm [HR 0.28; (95% CI, 0.19 to 0.41); *P*<0.001]. Median PFS for lorlatinib (Lorbrena) was not reached while that for crizotinib (Xalkori) was 9.3 months (95% CI; 7.6, 11.1). In an updated analysis from the CROWN study, after 5 years of follow-up, lorlatinib continued to show superior efficacy over crizotinib in patients with ALK+ NSCLC, with at a median follow-up of 60.2 months, median PFS was still NR with lorlatinib. Most (76%) PFS events occurred in the first 2 years with lorlatinib in the CROWN study, with only six additional PFS events occurring between 3 years and 5 years. At the time of this analysis in May 2024, the required number of OS events for a protocol-specified second interim analysis was not met. Overall survival (OS) follow-up is currently ongoing in the CROWN study.

VIII. ROS1 gene rearrangements occur in an estimated 1% - 2% of patients with NSCLC. The NCCN guidelines recommend crizotinib, entrectinib, or ceritinib as first-line monotherapy options for patients with ROS1+ metastatic NSCLC. Ceritinib (Zykadia) is an “other recommended” first-line therapy option for patients with ROS1+ metastatic NSCLC and provides a cost-effective treatment option. Crizotinib (Xalkori) is currently FDA-approved for ROS1+ NSCLC and ALK+ systemic ALCL.

Brigatinib (Alunbrig)

IX. Brigatinib (Alunbrig) was evaluated in an open-label, Phase 3, randomized trial against crizotinib (Xalkori) in metastatic ALK+ NSCLC. The study included 275 subjects, and those receiving brigatinib (Alunbrig) had a greater PFS (12-month PFS was 67% versus 43%; HR 0.49, p<0.001). The intracranial response was 78% for brigatinib (Alunbrig) and 29% for crizotinib (Xalkori). The data is not considered high quality due to open label trial design, and lack of clinically significant outcomes such as overall survival and quality of life parameters.

Ensartinib (Ensacove)

X. Ensartinib (Ensacove) is the sixth FDA-approved ALK inhibitor for the treatment of ALK-positive NSCLC and joins crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lobrena). Ensartinib (Ensacove) exhibits brain-penetrant properties like alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lobrena).

XI. Ensartinib (Ensacove) was studied in a Phase 3, open-label, randomized study (eXALT3). The study included 290 participants 18 years and older with confirmed locally advanced or metastatic ALK-positive NSCLC. Participants with prior ALK inhibitors were not permitted. Participants were randomized to receive ensartinib (Ensacove) 225mg orally once daily or crizotinib (Xalkori) 250mg orally twice daily. Baseline characteristics were similar between both groups: median age 54 years, mostly men (51%), Asian (56%), and never smokers (62%). The primary endpoint was PFS, which was significantly higher in the ensartinib (Ensacove) group compared to crizotinib (25.8 months vs 12.7 months, HR 0.51 (0.35, 0.72), p<0.001. Overall survival (OS) was not mature at the time of PFS analysis.

XII. There is currently no evidence that ALK-inhibitors improve clinical outcomes (e.g., overall survival, quality of life) in patients with NSCLC. Quality of life parameter improvements were reported in CROWN study for lorlatinib (Lorbrena). However, this improvement was not clinically significant. Although PFS data is promising, PFS is a surrogate endpoint in NSCLC that has not been correlated with improved outcomes.

XIII. 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.

XIV. Information on FDA-approved tests for the detection of ALK rearrangements in NSCLC is available at http://www.fda.gov/CompanionDiagnostics

Investigational or Not Medically Necessary Uses

I. The agents in this policy have not been sufficiently evaluated in the following settings. There may be NCCN recommendations or low-quality data available; however, safety and efficacy have not been established for:
   A. ALK+ systemic Anaplastic Large Cell Lymphoma (ALCL) in patients one year of age and older
      i. In January 2021, crizotinib (Xalkori) received expanded approval in patients aged one and older with ALK+ relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) based on a phase 2, open-label, single-arm study in 26 patients aged one to ≤ 21 years with ALK+ ALCL. All enrolled patients were refractory to systemic chemotherapy, two patients were refractory to a monoclonal antibody, and one patient was refractory to brentuximab. Primary outcome studied was objective response rate (ORR), which was 88% [95% CI 71-96]. There were 21 (81%) and 2 (8%) of patients who achieved complete response (CR) and partial response (PR), respectively. The median time to first response was 3.9 weeks (range: 3.5-9.1 weeks). Progression free survival and overall survival were not evaluated.

ii. The NCCN guidelines for peripheral T-cell lymphoma version 4.2024 recommend ALK+ Inhibitors (alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib) as other recommended regimens for the treatment ALK+ ALCL. Enrollment in clinical trial remains the preferred regimen for ALCL. There is currently no evidence that crizotinib (Xalkori) or other ALK inhibitors improves clinically meaningful outcomes (e.g., overall survival, quality of life) in patients with ALCL. Improvement in ORR has not been correlated with improved clinically meaningful outcomes. While Alectinib is approved for relapsed/refractory ALCL in Japan, crizotinib (Xalkori) and remaining ALK inhibitors remain an investigational treatment in all patients with ALCL.

B. Inflammatory myofibroblastic tumors (IMT)
   i. In July 2022, crizotinib (Xalkori) received FDA approval for the treatment of adult and pediatric patients one year and older with unresectable, recurrent, or refractory ALK+ IMT. The medication received the approval based on two clinical trials, one in the pediatric space and one in adults.
   ii. The efficacy of crizotinib (Xalkori) in pediatrics was evaluated in a multicenter, single-arm, open-label Phase 2 study in fourteen patients aged 1 to 21 with unresectable, recurrent, or refractory ALK+ IMT. Twelve patients had undergone prior therapy, most commonly surgery, but also chemotherapy and radiation. Twelve of the fourteen patients received 280mg/m^2 twice daily until disease progression or unacceptable toxicity; two patients received a lower dose. The primary endpoint was objective response rate (ORR); five patients attained a complete response and seven had a partial response.
   iii. The efficacy of crizotinib (Xalkori) in adults was evaluated in a multicenter, single-arm, open-label phase 1b study of seven patients with unresectable, recurrent, or refractory ALK+IMT. Patients received 250 mg twice daily in evaluation of the primary outcome of ORR. Of the seven patients, one patient had a complete response, five patients had a partial response, and the median duration of treatment was nearly three years in 67% of these patients.
   iv. The NCCN soft tissue sarcoma version 2.2024 guidelines recommend ALK+ Inhibitors (alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib)) as preferred category 2A regimens for the treatment of IMT with ALK+ translocation.
   v. Currently, there is no evidence that crizotinib (Xalkori) improves clinically meaningful outcomes (e.g., overall survival, quality of life) in patients with ALK+IMT. Improvement in ORR has not been correlated with improved clinically meaningful outcomes. ALK+ inhibitors remain an investigational treatment in all patients with ALK+IMT.

C. ROS1+ NSCLC for any agent in this policy except for crizotinib (Xalkori)
D. NSCLC outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
E. Erdheim-Chester Disease (ECD) with ALK fusion
   i. The NCCN recommends the use of ALK+ inhibitors (alectinib, brigatinib, ceritinib, crizotinib, and lorlatinib) for anaplastic lymphoma kinase (ALK)-fusion targeted symptomatic Erdheim-Chester Disease in certain circumstances. However their use in histiocytic neoplasms like ECD has not been evaluated for efficacy and safety in phase III clinical trials.
F. Large B-Cell Lymphoma (LBCL)
G. NSCLC in combination with other therapies
H. Thyroid cancer

I. Melanoma
J. Gastrointestinal cancer
K. Prostate cancer
L. Leukemias or lymphomas
M. Urothelial cancer

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References

1. Lorbrena [Prescribing Information]. New York, NY: Pfizer, April 2023.
2. Xalkori [Prescribing Information]. New York, NY: Pfizer, September 2023
3. Zykadia [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals, October 2021.
4. Alunbrig [prescribing information]. Cambridge, MA: Ariad Pharmaceutical. February 2022.
5. Alecensa [prescribing information]. San Francisco, CA: Genentech USA, Inc. April 2024.
6. NCCN: NCCN Non-Small Cell Lung Cancer Guidelines Versions 3.2025 – January 14, 2025
7. NCCN Guidelines for the treatment of T-Cell Lymphomas. Version 4.2024. National Comprehensive Cancer Network. Available at: https://www.nccn.org/.
8. NCCN Guidelines for the treatment of Soft Tissue Sarcoma Version 2.2024 National Comprehensive Cancer Network. Available at: https://www.nccn.org/..
9. NCCN Guidelines for the treatment of Histiocytic Neoplasms Version 2.2024. National Comprehensive Cancer Network. Available at: https://www.nccn.org/.
10. Up To Date. Uncommon Sarcoma Subtypes, Inflammatory Myofibroblastic Tumor; updated August 24, 2022.
11. Bauer T., Besse B., Solomon, B., et at. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol. 2018. 19: 1654-1667
12. Xcovery Holding Company LLC. Study comparing X-396 (ensartinib) to crizotinib in ALK positive non-small-cell lung cancer (NSCLC) patients. U.S. National Library of Medicine Clinical Trials website. https://clinicaltrials.gov/ct2/show/NCT02767804. May 22, 2017. Accessed December 21, 2017.
13. European Society. ELCC 2017 News: ensartinib demonstrates CNS activity in ALK-positive NSCLC patients. European Society for Medical Oncology website. http://www.esmo.org/Conferences/Past-Conferences/ELCC-2017-Lung-Cancer/News-Press-Releases/Ensartinib-Demonstrates-CNS-Activity-in-ALK-positive-NSCLC-Patients. May 06, 2017. Accessed December 21, 2017.
14. Pfizer. A study of pf-06463922 an ALK/ROS1 inhibitor in patients with advance non-small-cell lung cancer with specific molecular alterations. U.S. National Library of Medicine Clinical Trials website. https://clinicaltrials.gov/ct2/show/NCT01970865. November 22, 2017. Accessed December 21, 2017.
15. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2017.
16. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med*. 2014;371(23):2167-77.
17. Soria JC, Tan DS, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomized, open-label, phase 3 study. *Lancet*. 2017;389(10072):917-929.
18. Gadgeel SM, Shaw AT, Govindan R, et al. Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients with ALK-Positive Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2016;34(34):4079-4085.
19. Gadgeel S, Shaw AT, Barlesi F, et al. Cumulative incidence rates for CNS and non-CNS progression in two phase II studies of alectinib in ALK-positive NSCLC. *Br J Cancer*. 2018;118(1):38-42.
20. Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(7):874-886.
21. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in Patients with Crizotinib-Refractory Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer: A Randomized, Multicenter Phase II Trial. *J Clin Oncol*. 2017:JCO2016715904.

22. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018;379(21):2027-2039.
23. Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, Mazieres J, Kim DW, Mok T, Polli A, Thurm H, Calella AM, Peltz G, Solomon BJ; CROWN Trial Investigators. First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer. N Engl J Med. 2020 Nov 19;383(21):2018-2029. doi: 10.1056/NEJMoa2027187. PMID: 33207094.
24. Mossé YP, Voss SD, Lim MS, et al. Targeting ALK With Crizotinib in Pediatric Anaplastic Large Cell Lymphoma and Inflammatory Myofibroblastic Tumor: A Children's Oncology Group Study. J Clin Oncol. 2017;35(28):3215-3221. doi:10.1200/JCO.2017.73.4830
25. Foster JH, Voss SD, Hall DC, et al. Activity of Crizotinib in Patients with ALK-Aberrant Relapsed/Refractory Neuroblastoma: A Children's Oncology Group Study (ADVL0912). Clin Cancer Res. 2021 Jul 1;27(13):3543-3548. doi: 10.1158/1078-0432.CCR-20-4224. Epub 2021 Feb 10. PMID: 33568345; PMCID: PMC8254744.
26. Gambacorti-Passerini C, Orlov S, Zhang L et al. Long-term effects of crizotinib in ALK-positive tumors (excluding NSCLC): A phase 1b open-label study. Am J Hematol. 2018 May;93(5):607-614. doi: 10.1002/ajh.25043. Epub 2018 Feb 8. PMID: 29352732; PMCID: PMC5947833.
27. Hotta K, Hida T, Nokihara H, et al. Final overall survival analysis from the phase III J-ALEX study of alectinib versus crizotinib in ALK inhibitor-naïve Japanese patients with ALK-positive non-small-cell lung cancer. *ESMO Open*. 2022;7(4):100527. doi:10.1016/j.esmoop.2022.100527
28. Shaw AT, et al. Alectinib in ALK positive, crizotinib resistant, non small cell lung cancer: a single group, multicentre, phase 2 trial. Lancet Oncol 2016;17:234-242
29. Hida T, et al. Alectinib versus crizotinib in patients with ALK-positive non-smallcell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390:29-39.
30. Ou SI, et al. Alectinib in crizotinib refractory ALK rearranged non small cell lung cancer: a phase II global study. J Clin Oncol 2016;34:661-668
31. Naito T, Shiraishi H, Fujiwara Y. Brigatinib and lorlatinib: their effect on ALK inhibitors in NSCLC focusing on resistant mutations and central nervous system metastases. *Jpn J Clin Oncol*. 2021;51(1):37-44. doi:10.1093/jjco/hyaa192
32. Lim SM, et al. Open-label, multicenter, phase II study of ceritinib in patients with non-small-cell lung cancer harboring ROS1 rearrangement. J Clin Oncol 2017;35:2613-2618.
33. Shaw AT, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 2014;371:1963-1971.
34. Solomon BJ, Liu G, Felip E, et al. Lorlatinib Versus Crizotinib in Patients With Advanced *ALK*-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. *J Clin Oncol*. Published online May 31, 2024. doi:10.1200/JCO.24.00581
35. Ensacove (ensartinib) [prescribing information]. Miami, FL: Xcovery Holdings Inc; December 2024.
36. Horn L, Wang Z, Wu G, et al. Ensartinib vs Crizotinib for Patients With Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer: A Randomized Clinical Trial. JAMA Oncol. 2021;7(11):1617-1625.

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
entrectinib (Rozlytrek)	ROS1+ metastatic NSCLC
repotrectinib (Augtyro)	ROS1+ metastatic NSCLC, NRTK fusion solid tumors

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria and supporting evidence for ensartinib (Ensacove) for treatment of ALK+NSCLC (newly FDA approved October 2024).	05/2025
Removed step through alectinib as the preferred treatment option in advance/metastatic NSCLC. Added criteria for alectinib for adjuvant treatment of ALK+ NSCLC. Added certinib as a treatment option in ROS1+ NSCLC. Updated requirements for lorlatinib in ALK+ NSCLC. Removed oncologist specialist requirement in renewal. Updated supporting evidence, E/I, references, related policies.	09/2024
Added expanded indication for crizotinib (Xalkori) for ALK+ IMT as investigational and updated quantity limit table to include this indication	04/2023
Updated supporting evidence around alectinib being the preferred first-line therapy	11/2021

Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Added expanded indication for lorlatinib (Lorbrena) in the first-line treatment setting; added indication of ALK+ systemic ALCL for crizotinib (Xalkori) as investigational, updated quantity level limits for crizotinib (Xalkori), updated the supporting evidence section to include crizotinib (Xalkori) in the setting of ALK+ systemic ALCL	04/2021
Criteria update: Transitioned prior authorization criteria to policy format and consolidated all agents into one policy. Brigatinib now allowed for first-line setting if member has CI or intolerance to preferred therapy. Quantity level limits updated to reflect currently available products and package sizes. Addition of Zykadia tablets that are available in addition to the capsules.	07/2019
Criteria updates: Crizotinib updated criteria to new format, moved new start versus continuation question up. Updated prescriber question to fit current format, updated and added a question regarding both of the FDA-approved indications. Added a question regarding other therapies tried and failed or contraindicated. Zykadia updated to new format, deleted try and fail crizotinib question as this agent can now be used first line, added try and fail alectinib question, as per class review this is Moda Health's preferred agent. Removed age question, removed LFT question, QT prolongation question, and placed new versus continuation question up front. Alecensa criteria updated criteria to new format, deleted try and fail crizotinib question as this agent can now be used first line, removed age question. Alunbrig criteria updated to add question regarding prescribed and preferred therapy.	01/2018
Past criteria reviews	12/2012, 09/2014, 12/2015, 06/2017
Criteria created	12/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP003

Split Fill Management* [Applies to alpelisib (Piqray) ONLY]

Description

Alpelisib (Piqray, Vijoice) is an orally administered kinase inhibitor with predominant activity against PIK3CA gene.

Length of Authorization

- Initial: Six months (first three months split fill for alpelisib [Piqray] only)
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit*
alpelisib (Piqray)	Advanced or metastatic breast cancer, PIK3CA mutation positive, HR+, HER2-	150 mg tablets (300 mg daily dose pack)	56 tablets/28 days
		200 mg tablets (200 mg daily dose pack)	28 tablets/28 days
		200 mg and 50 mg tablets (250 mg daily dose pack)	56 tablets/28 days
alpelisib (Vijoice)	PIK3CA-Related Overgrowth Spectrum (PROS)[Ŧ, **]	50 mg tablets (50 mg daily dose pack)	28 tablets/28 days
		125 mg tablets (125 mg daily dose pack)	28 tablets/28 days
		200 mg and 50 mg tablets (250 mg daily dose pack)	56 tablets/28 days

***Quantity limit exceptions not allowed, except for dose reductions.**

[Ŧ]Experimental/ Investigational indication.

*****Disclaimer: In the event an exception is granted for alpelisib (Vijoice) for any condition, a trial of a comparable, cost-effective formulation of alpelisib will be required [i.e., alpelisib (Piqray)].***

Initial Evaluation

I. **Alpelisib (Piqray)** may be considered medically necessary when the following criteria 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; **AND**
   C. A diagnosis of **advanced or metastatic breast cancer; AND**
      1. The request is for alpelisib (Piqray); **AND**
      2. The breast cancer is HR-positive, HER2-negative; **AND**
      3. PIK3CA mutation has been tested and confirmed; **AND**
      4. Provider attestation that the member is endocrine resistant or refractory; **AND**
      5. The medication will be used in combination with fulvestrant (Faslodex) only; AND

6. Alpelisib (Piqray) will not be used in combination with any other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]

II. Alpelisib (Piqray) is considered not medically necessary when the criteria above are not met and/or when used for:
   A. Breast cancer that is not PIK3CA mutated.

III. Alpelisib (Piqray, Vijoice) is considered investigational when used for all other conditions, including but not limited to:
   A. PIK3CA- Related Overgrowth Spectrum (PROS)
   B. Overgrowth Spectrum disorders without PIK3CA mutation
   C. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
   D. Meningioma
   E. Oropharyngeal cancer
   F. Melanoma
   G. Renal cell cancer
   H. Pancreatic cancer
   I. Head and neck cancers
   J. Ovarian 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. Alpelisib (Piqray) will be used in combination with fulvestrant (Faslodex); **AND**
   A. Alpelisib (Piqray) will not be used in combination with any other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]; **AND**
IV. Member has exhibited a positive response to treatment or stability of disease symptoms (e.g., stabilization of disease, a decrease in tumor size or tumor spread)

Supporting Evidence

I. Alpelisib (Piqray, Vijoice) is an orally administered kinase inhibitor with predominant activity against PIK3CA gene. It is FDA-approved for the treatment of advanced or metastatic breast cancer with PIK3CA mutation, and for PIK3CA-Related Overgrowth Spectrum (PROS). The FDA approvals for these indications are specific to the respective formulation of alpelisib as well as recommended dosing. Alpelisib (Piqray) is indicated for the treatment of breast cancer, and alpelisib (Vijoice) is indicated for the treatment of PROS. Of note, use of alpelisib (Vijoice) for the treatment of PROS is considered experimental and investigational (please see the experimental and investigational section below).

II. Given the complexities involved with the diagnosis, treatment approaches and management of therapy for the indicated population, the treatment with alpelisib (Piqray) should be initiated by or in consultation with an oncologist.

III. Alpelisib (Piqray) was evaluated in one double-blind, Phase 3, placebo-controlled randomized trial (SOLAR-1). Both arms were in combination with fulvestrant. The trial evaluated adult subjects with and without the PIK3CA mutation; however, those without the mutation did not show favorable outcomes; thus, the efficacy information stated here is specific to those with the PIK3CA mutation. Safety information was pulled from the entirety of the population.

IV. Subjects in the pivotal trial had HR+, HER2-, advanced or metastatic breast cancer; 98% of which had received prior endocrine therapy and were deemed to be endocrine resistant. The trial focused on the endocrine-refractory population. The primary efficacy outcome was progression free survival (PFS), and secondary outcomes included PFS per a blinded review committee, overall response (OR) and clinical benefit (CB) (i.e., complete or partial response or stable disease). The primary outcome, PFS, was 11 months versus 5.7 months for alpelisib (Piqray) plus fulvestrant versus placebo plus fulvestrant (HR 0.65, $p<0.001$). Overall response was 26.6% versus 12.8% respectively, and CB was 61.5% versus 45.3% respectively.

V. There is a high risk of serious adverse events with alpelisib (Piqray). Serious adverse events occurred in 34.9% versus 16.7% for the placebo group. Adverse events of serious grade that occurred more often in the alpelisib (Piqray) arm versus placebo included: hyperglycemia, diarrhea, abdominal pain, acute kidney injury, anemia, nausea, osteonecrosis of the jaw, rash, stomatitis, erythema multiforme, hypokalemia, mucosal inflammation, maculopapular rash, creatinine increased, brain edema, renal failure, bacteremia, Steven's Johnson Syndrome, and many other cases of serious safety concerns. Common adverse reactions occurring in more than 20% of subjects included laboratory abnormalities (glucose, creatinine, lymphocyte, GGT, ALT, lipase, calcium, hemoglobin), fatigue, decrease appetite, stomatitis, vomiting, weight loss, aPTT prolongation, and alopecia. Tolerability of alpelisib (Piqray) is of concern; 74% of subjects from the treatment arm in SOLAR-1 required a dose-interruption and 64% required a dose-reduction versus 32% and 9% for the placebo arm respectively. Permanent discontinuation of drug due to adverse events occurred in 25% of alpelisib (Piqray) subjects versus 4.2% for subjects in the placebo group.

VI. The safety and efficacy of alpelisib (Piqray) in patients with HR+, HER2-, advanced or metastatic breast cancer with PIK3CA mutation and prior CDK4/6 inhibitor use has not been extensively studied due to evolving standard of care to include front-line use of CDK4/6 inhibitors. Nevertheless, the use of alpelisib (Piqray) may be supported in this setting by a small number of patients included in the SOLAR-1 trial, a Phase 2, open-label trial, BYLieve, as well as several non-interventional, retrospective studies which demonstrate modest efficacy and comparable safety in the real-world setting.

Investigational or Not Medically Necessary Uses

I. PIK3CA-Related Overgrowth Spectrum (PROS):
*** Disclaimer: In the event an exception is granted for alpelisib (Vijoice) for any condition, a trial of a comparable, cost-effective formulation of alpelisib will be required [i.e., alpelisib (Piqray)].*

A. Alpelisib (Vijoice) received accelerated FDA-approval and a breakthrough therapy designation for the treatment of PIK3CA-related overgrowth spectrum (PROS) in patients two years of age and older, who require systemic therapy. This approval was based on the data of an open-label, retrospective chart review study, and continued approval remains contingent upon confirmatory trials.

B. Alpelisib (Vijoice) is available as monthly therapy packs consisting of 50 mg, 125 mg and 200 mg tablets. The recommended dose of alpelisib (Vijoice) is 250 mg once daily for adults. For pediatric patients, the dose is age dependent. For children 2 to 6 years of age: 50 mg once a day; and for children ≥6 years of age and adolescents <18 years of age: initial dose of 50 mg daily for 6 months, followed by dose titration to 125 mg once a day to optimize clinical response.
C. As of September 2022, the monthly cost of alpelisib (Vijoice) remains significantly higher (>2 fold) than that of comparable formulations (therapy packs) of alpelisib (Piqray). In the event an exception is granted for alpelisib (Vijoice) for the treatment of PROS, alpelisib (Piqray) may serve as a comparable cost-effective formulation.
D. According to the prescribing information for alpelisib (Piqray, Vijoice), there is no well-established maximum dose for the approved indications. It is expected that alpelisib (Vijoice) may be utilized at higher doses in order to optimize clinical response. Availability of alpelisib (Piqray) therapy packs consisting of alpelisib (Piqray) 50 mg, 150 mg, and 200 mg tablets, may provide an avenue for dose escalations and optimizations. As an example, for an adult member requiring 250 mg daily dose of alpelisib (Vijoice), a 250 mg daily dose pack of alpelisib (Piqray) may be considered as an alternative. Similarly, a provider outreach may be needed in order to achieve optimized dosing for adolescent members, for whom the recommended daily dose of alpelisib (Vijoice) is 125 mg. It is estimated that these members may see dose escalations to 150 mg or beyond. In absence of concerns regarding drug toxicity, a daily dose of 150 mg may be efficacious alternative to a 125 mg daily dose.
E. PIK3CA-related overgrowth spectrum (PROS) is a heterogeneous group of rare, asymmetric overgrowth disorders caused by postzygotic variants in the PIK3CA gene. One PIK3CA encodes the p110α catalytic subunit of phosphoinositide 3-kinase (PI3K), which transduces activation of tyrosine kinase growth factor and hormone receptors into activation of AKT and mTOR signaling to promote tissue growth.
F. Overgrowth includes adipose tissue, muscle, skin, bone, blood or lymph vessels, or neural tissue, among others. Adipose and vascular components are particularly striking, reflecting the inherent plasticity and postnatal growth potential of these tissues. Complications of PROS depend on the anatomical site and extent of overgrowth, but may include functional impairment (e.g., of walking or swallowing), pain, recurrent superficial infections, thromboembolism, and/or hemorrhage, all of which may be debilitating, and cause early mortality. Based on the organ system involvement and the types of lesions, PROS may present as heterogeneous segmental overgrowth phenotypes - with or without vascular anomalies. Some of the prominent anomalies classified under PROS include CLOVES Syndrome, Klippel-Trenaunay Syndrome (KTS), Fibroadipose Infiltrating Lipomatosis (FIL), and Megalencephaly-Capillary Malformation (MCAP, or M-CM).
G. Current standard of care for PROS involves regular monitoring, debulking surgery, amputation, and/or endovascular occlusive procedures. Regrowth following surgery occurs frequently and repeated surgery is common.
H. Allosteric mTOR inhibitors such as sirolimus, which is approved for posttransplant immunosuppression, have been utilized for PROS treatment. Sirolimus may potently attenuate pathological AKT signaling and reduces cell proliferation in dermal fibroblasts derived from people with PROS, which suggests that it could be an effective treatment of PROS. However, it is important to note that the use of sirolimus may only be applicable to the patient population, whose PROS involves vascular and lymphatic malformations with predominant adipose overgrowth. These lesions are typically seen in CLOVES syndrome,

FIL, and MCAP, and manifest as visible lesions on the contralateral limb, truncal region, and/or face. In absence of these anomalies, the use of sirolimus may be deemed inappropriate by the treating provider.

I. A non-randomized, single-arm, open-label clinical trial (N=39) assessed the efficacy and safety of low-dose sirolimus (median target plasma levels of 3.3 ng/mL). Patients aged from three years to 65 years were included. For the primary outcome, tissue volumes at affected and unaffected sites were measured by dual-energy X-ray absorptiometry during 26 weeks of untreated run-in and 26 weeks of sirolimus therapy. Among the 30 participants, who completed the study, sirolimus led to a change in mean percentage total tissue volume of –7.2% (SD 16.0, p 0.04) at affected sites, but not at unaffected sites (+1.7%, SD 11.5, p 0.48) (n = 23 evaluable). No differences were detected in QOL scores before and after sirolimus treatment among adults or children. During run-in, five hospitalizations in five participants and two surgical interventions in two participants were recorded. In the treatment phase 15 hospitalizations in 9 participants and no surgical interventions arose. This difference was not significant (p = 0.24). Twenty-eight of 39 (72%) participants had ≥1 adverse event related to sirolimus of which 37% were grade 3 or 4 in severity and 7/39 (18%) participants were withdrawn consequently.

J. Efficacy of alpelisib (Vijoice) was evaluated using real-world data from EPIK-P1, a single-arm, open-label retrospective chart review study in patients, who received alpelisib (Vijoice) as part of an expanded access program for compassionate use. Eligible patients had clinical manifestations of PROS that were assessed by the treating physicians as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene. The efficacy of alpelisib (Vijoice) was evaluated in a total of 37 patients with at least one target lesion identified on imaging performed within 24 weeks prior to receipt of the first dose. The major efficacy outcome measure was the proportion of patients with a radiological response at week 24 as determined by blinded independent central radiology review, defined as a ≥20% reduction from baseline in the sum of measurable target lesion volume in up to 3 lesions confirmed by at least 1 subsequent imaging assessment. Duration of response was an additional efficacy outcome measure. Of the 37 patients included in the efficacy population, 27% (95% CI: 14, 44) had a radiological response at week 24. The most common (≥10%) adverse reactions occurring in patients were diarrhea, stomatitis, and hyperglycemia. Additionally, improvements in functionality were observed as determined by Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale and Lansky and Karnofsky scales: at baseline, the performance status was recorded for 47 patients: at the 24 weeks follow-up, 30% of patients showed ECOG PS improvement of at least 1 point and Karnofsky scale at least 20 points.

K. Despite accelerated approval and orphan designation, continued approval of alpelisib (Vijoice) remains contingent upon the verification of clinical benefit in confirmatory trials. Although FDA-approved for the treatment of PROS, efficacy data for alpelisib (Vijoice) is based on a retrospective chart review of a small patient population. The quality of data is considered low and the true clinical value of alpelisib (Vijoice) for the treatment of PROS remains undetermined.

L. Given the lack of curative therapy options and paucity of clinical data supporting the use of currently approved therapies, enrollment in a clinical trial may remain a practical management approach for patients with PROS. 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 diseases with limited or no treatment options. As of September 2022, alpelisib (Vijoice) is available to patients via ongoing clinical trial and an expanded access program across the US and other countries.

II. Breast cancer without PIK3CA mutation.
    A. Alpelisib (Piqray) was evaluated in breast cancer patients that did not have the PIK3CA mutation and statistical significance over placebo was not reached.
III. Aleplisib (Piqray, Vijoice) is currently being investigated for safety and efficacy in many oncolytic disease states and potentially other non-oncolytic conditions. Safety and efficacy have not yet been determined in the following:
    A. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
    B. Meningioma
    C. Oropharyngeal cancer
    D. Melanoma
    E. Renal cell cancer
    F. Pancreatic cancer
    G. Head and neck cancers
    H. Ovarian 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. Piqray [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. June 2019.
2. National Comprehensive Cancer Network. NCCN Guidelines: Breast Cancer V5.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated July 15, 2020.
3. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for -Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019;380(20):1929-1940.
4. Rugo HS et al. Alpelisib + fulvestrant in patients with PIK3CAmutated hormone-receptor positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDKi) + aromatase inhibitor (AI): BYLieve study results. Oral presentation at: American Society of Clinical Oncology (ASCO); May 29 - May 31, 2020; Chicago, IL. Presentation 1006.
5. Canaud G, et al. EPIK-P1: Retrospective Chart Review Study of Patients With PIK3CA-Related Overgrowth Spectrum Who Have Received Alpelisib as Part of a Compassionate Use Programme. Presented at the 2021 ESMO Congress; September 17-21, 2021.
6. Alpelisib (Vijoice) prescribing information, Novartis Pharmaceutical Corp.,East Hanover, NJ, USA. April 2022.
7. Alpelisib (Vijoice) clinical trial data (unpublished). https://www.hcp.novartis.com/products/vijoice/pik3ca-related-overgrowth-spectrum/efficacy/.

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

Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer, HER2-negative, HR-positive, advanced, or metastatic

Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of criterion requiring CDK4/6 inhibitor naïve patient population from the metastatic breast cancer indication	08/2023
Inclusion of new indication for PROS in the QL table; added PROS as E/I indication; added supporting evidence for PROS; format changes to align with current policy format	11/2022
Updated supporting evidence section to include data from BYLieve clinical trial	09/2020
Policy created	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP030

Description

Amifampridine (Firdapse, Ruzurgi) are orally administered, broad-spectrum potassium channel blockers.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
amifampridine (Firdapse)	Lambert-Eaton myasthenic syndrome	10 mg tablets	240 tablets/30 days
amifampridine (Ruzurgi)*		10 mg tablets	240 tablets/30 days

**In a January 2022 court ruling, the FDA converted the final approval of the Ruzurgi new drug application to a tentative approval. Therefore, Ruzurgi may not be legally marketed or distributed in the United States at this time*

Initial Evaluation

I. Amifampridine (Firdapse, Ruzurgi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, a neurologist; **AND**
   B. A diagnosis of **Lambert-Eaton Myasthenic Syndrome (LEMS)**; **AND**
      a. Documentation of a confirmatory diagnostic test:
         i. Repetitive Nerve Stimulation (RNS); **OR**
         ii. Positive anti-P/Q type voltage-gated calcium channel (VGCC) antibody test; **AND**
      b. Member is experiencing moderate to severe weakness that interferes with function

II. Amifampridine (Firdapse, Ruzurgi) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
   A. Inflammatory muscle disease
   B. Limb-girdle muscular dystrophy
   C. Myasthenia gravis
   D. Congenital myasthenic syndrome
   E. Motor neuron disease (i.e. amyotrophic lateral sclerosis, multifocal motor neuropathy)

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., improved muscle strength

Supporting Evidence

I. LEMS is a rare presynaptic disorder of neuromuscular transmission in which the release of acetylcholine is impaired. Disruption of a subset of P/Q-type CA2+ channels causes proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation, and autonomic dysfunction. Major clinical presentation is progressive proximal muscle weakness. Forty to 60% of LEMs cases are paraneoplastic, involving and correlated with a [usually new] cancer diagnosis. Remaining patients with autonomic LEMS and without cancer, expect normal longevity.
II. Patients with LEMS who have mild weakness that does not interfere with function can be monitored without the use of symptomatic or immunologic therapy. Amifampridine (also known as 3,4-diaminopyridine) is the recommended therapy in patients with moderate or severe weakness that interferes with functions of daily living. Guanidine is approved for the treatment of LEMS, however, is associated with a high-level of toxicity and adverse effects, limiting its use. Pyridostigmine is known to be less toxic overall and is sometimes taken as in conjunction with guanidine. Use of pyridostigmine is generally accepted if amifampridine is not accessible, however its use is not supported by high-quality data. When used as monotherapy it has been shown to be only mildly effective with no effect on muscle strength. Immunoglobulin is often used in patients specifically for refractory weakness, which may or may not be associated with the underlying cancer in paraneoplastic LEMS. Alternative immunotherapies used include prednisone, azathioprine, plasma exchange, mycophenolate, rituximab.
III. In trials LMS-002, LMS-003, and DAPPER, subjects were confirmed of diagnosis of LEMS by nerve conduction findings OR positive anti-P/Q type voltage-gated calcium channel (VGCC) antibody test. This appears to be aligned with practice as the diagnosis is made via clinical features (e.g., muscle weakness, autonomic dysfunction, ptosis and diplopia) and electrodiagnostic studies (e.g., VGCC or repetitive nerve stimulation) as confirmatory evidence.
IV. The clinical presentation of LEMS that of slowly progressive, symmetric and proximal weakness, among other clinical symptoms, indicates a need of specific diagnosis by an experienced specialist.
V. There is a lack of strong scientific evidence to support the safety and efficacy for an increased dosing frequency or doses above the recommended. Trials were too small to indicate a dose-related trend of improvement or indicate a variation in effectiveness among subgroup populations.

Investigational or Not Medically Necessary Uses

I. Diagnosis of LEMS is largely based on clinical assessment and rule-out of other symptomatically similar disease. The following disease states have a similar presentation or relatedness to LEMS, however, randomized controlled trials to support the efficacy and safety of amifampridine (Firdapse, Ruzurgi) have yet to be completed.
   A. Inflammatory muscle disease
   B. Limb-girdle muscular dystrophy
   C. Myasthenia gravis
   D. Congenital myasthenic syndrome
   E. Motor neuron disease (i.e. amyotrophic lateral sclerosis, multifocal motor neuropathy)

References

1. Firdapse [prescribing information]. Coral Gables, FL: Catalyst Pharmaceuticals; February 2021.
2. Ruzurgi [prescribing information]. Plainsboro, NJ: Jacobson Pharmaceutical Company; May 2019.
3. FDA. Center for Drug Evaluation and Research. Application number: 208078Orig1s000 Summary Review. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/208078Orig1s000SumR.pdf. Accessed December 21, 2018.
4. FDA. Center for Drug Evaluation and Research. Application number: 209321Orig1s000 Summary Review.
5. UpToDate, Inc. Lambert-Eaton myasthenic syndrome: Clinical features and diagnosis. UpToDate [Online Database]. Waltham, MA. Last updated July 15, 2021. Available from: http://uptodate.com/home/index.html. Accessed March 21, 2022.
6. UpToDate, Inc. Lambert-Eaton myasthenic syndrome: Treatment and prognosis. UpToDate [Online Database]. Waltham, MA. Last updated January 07, 2021. Available from: http://uptodate.com/home/index.html. Accessed March 21, 2022.
7. GuaTitulaer MJ, Lang B, Verschuuren J. Lambert–Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol. 2011;10:1098-107.
8. Guanidine [prescribing information]. Whitehouse Station, NJ: Merck Sharp & Dohme; November 2017.
9. FDA. Letter to Jacobus Pharmaceutical Company, Inc: Conversion to NDA Tentative Approval. February 01, 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/209321Orig1s000TA_ltr.pdf

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of requirement to trail Ruzurgi prior to Firdapse due to removal of Ruzurgi from market. In a January 2022 court ruling, the FDA converted the final approval of the Ruzurgi new drug application to a tentative approval. Therefore, Ruzurgi may not be legally marketed or distributed in the United States at this time. Addition of criteria requiring symptomatic disease. Removal of initial criteria requiring trial of pyridostigmine or IVIG. Updated renewal section to include samples language and previous approvals.	04/2022
Addition of Ruzurgi to policy	07/2019
Policy created	02/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP201

Description
Amikacin liposomal (Arikayce) is an aminoglycoside antibiotic administered via nebulizer with the Lamira™ Nebulizer System

Length of Authorization
- Initial: Six months
- Renewal: Twelve months

Quantity limits

amikacin liposomal (Arikayce)	Indication	Quantity Limit	*DDID*
590 mg/8.4 mL suspension	*Mycobacterium avium* complex	252 mL/30 day	204273

Initial Evaluation

I. Amikacin liposomal (Arikayce) may be considered medically necessary when the following criteria are met:
   A. Prescribed by an infectious disease specialist; **AND**
   B. Patient is 18 years of age; **AND**
   C. A diagnosis of refractory *Mycobacterium avium* complex (MAC) lung disease as confirmed by a MAC-positive sputum culture when the following are met:
      1. Positive sputum culture obtained after at least six months of compliant use of a multi-drug regimen for MAC lung disease such as clarithromycin (or azithromycin), rifampin, and ethambutol within the past 12 months; **AND**
      2. Will be used as part of a multi-drug regimen; **AND**
      3. HIV negative

II. Amikacin liposomal (Arikayce) is considered investigational when used for all other conditions, including but not limited to:
   A. Cystic fibrosis patients with *Pseudomonas aeruginosa*
   B. Non-refractory MAC lung disease
   C. Use of amikacin liposomal (Arikayce) alone

Renewal Evaluation

I. Received therapy with amikacin liposomal (Arikayce) as part of a multi-drug regimen; **AND**
II. Has not received or will not receive 18 months or more of therapy with amikacin liposomal (Arikayce); **AND**
III. Negative sputum culture obtained within the last 30 days; **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

IV. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Amikacin liposomal (Arikayce)is FDA-approved as part of a combination regimen for the treatment of treatment of MAC lung disease in adults who do not achieve negative sputum cultures after 6 months of a multidrug background regimen therapy.

II. As per the package insert: Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Clinical benefit has not yet been established due to uncertainties with sputum culture conversion predicting clinical benefit in this patient population. As only limited clinical safety and effectiveness data for Arikayce is currently available, use should be reserved to adults who have limited or no alternative treatment options.

III. In the pivotal trial leading to approval, patients with a diagnosis of cystic fibrosis or HIV were excluded. The study met the primary efficacy outcome of culture conversion (three consecutive monthly negative sputum cultures) by month six.

IV. Per ATS/ISDA guidelines, the goals of therapy include symptomatic, radiographic, and microbiologic improvement. The primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy; therefore, sputum must be collected from patients throughout treatment. Patients should show clinical improvement within 3 to 6 months and should convert their sputum to negative within 12 months on macrolide-containing regimens. Failure to respond in these time periods should prompt investigation for possible noncompliance (perhaps due to drug intolerance) or macrolide resistance or the presence of anatomic limitations to successful therapy (e.g., focal cystic or cavitary disease).

V. Recent genotyping studies support 12 months of culture-negative sputum as a reasonable treatment endpoint because new positive sputum cultures for MAC after initial sputum conversion and culture negativity for 10 to 12 months are usually due to reinfection (new MAC genotype) rather than disease relapse.

VI. The ATS/IDSA guidelines state that patients should continue to be treated until they have negative cultures for one year. Patients that have had negative cultures for 1 year will not be approved for continued treatment.

VII. Treatment beyond the first renewal approval (after 18 months) will not be approved as amikacin liposomal (Arikayce) has not been studied beyond 18 moths nor in the reinfection or disease relapse setting.

Investigational or Not Medically Necessary Uses

I. Cystic fibrosis patients with *Pseudomonas aeruginosa*
   A. Use in cystic fibrosis patients with *Pseudomonas aeruginosa* was evaluated in a phase 3 study (NCT01315678), comparing amikacin liposomal (Arikayce) to inhaled tobramycin (Tobi). Results from the study are not yet available.

II. Non-refractory MAC lung disease

A. Per FDA label, the use of Arikayce is not recommended for patients with non-refractory MAC lung disease. Arikayce has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.

III. Use of amikacin liposomal (Arikayce) alone

A. In the pivotal trial leading to approval amikacin liposomal (Arikayce) was studied as part of a multi-drug regimen for treatment of refractory MAC. Monotherapy treatment with amikacin liposomal (Arikayce) is not supported by clinical evidence.

References

1. FDA approves a new antibacterial drug to treat a serious lung disease using a novel pathway to spur innovation [FDA Press Release]. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622048.htm.
2. Insmed Announces FDA Approval of ARIKAYCE® (amikacin liposome inhalation suspension), the First and Only Therapy Specifically Indicated for the Treatment of Mycobacterium Avium Complex (MAC) Lung Disease in Adult Patients with Limited or No Alternative Treatment Options [press release]. Available at: http://investor.insmed.com/news-releases/news-release-details/insmed-announces-fda-approval-arikaycer-amikacin-liposome.
3. Daley, DL. Mycobacterium avium Complex Disease. Microbiol Spectrum.April 2017. 5(2):TNMI7-0045-2017.
4. UpToDate, Inc. Overview of nontuberculous mycobacterial infections in HIV-negative patients. UpToDate [database online]. Waltham, MA. Last updated Oct 08, 2017 Available at: http://www.uptodate.com/home/index.html.
5. UpToDate, Inc. Epidemiology of nontuberculous mycobacterial infections. UpToDate [database online]. Waltham, MA. Last updated Apr 06, 2017 Available at: http://www.uptodate.com/home/index.html. Accessed
6. Griffith DE, Aksamit T, Brown-Elliot BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. February 2015; 175(4):367-416.
7. Griffith DE, Eagle G, Thomson R, et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Mycobacterium avium Complex (CONVERT): A Prospective, Open-Label, Randomized Study. Am J Respir Crit Care Med. September 2018; epub ahead of print.
8. FDA Briefing Document: Amikacin liposome inhalation suspension (ALIS) Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC). Updated August 7, 2018. Available at: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM615721.pdf.

Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

Amyloid Cardiomyopathy

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP034

Description

Acoramidis (Attruby), tafamidis meglumine (Vyndaqel), and tafamidis (Vyndamax) are orally administered transthyretin stabilizers.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
acoramidis (Attruby)	Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis	356 mg tablets	112 tablets/28 days
tafamidis meglumine (Vyndaqel)		20 mg capsules	120 capsules/30 days
tafamidis (Vyndamax)		61 mg capsules	30 capsules/30 days

Initial Evaluation

I. **Acoramidis (Attruby), tafamidis meglumine (Vyndaqel), or tafamidis (Vyndamax)** 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 cardiologist; **AND**
   C. Medication will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e., inotersen (Tegsedi), patisiran (Onpattro), eplontersen (Wainua), acoramidis (Attruby), tafamidis meglumine (Vyndaqel), tafamidis (Vyndamax)]; **AND**
   D. A diagnosis of **cardiomyopathy of wild type (wATTR-CM) or hereditary transthyretin-mediated amyloidosis (hATTR-CM)** when the following are met:
      1. Normal serum kappa/lambda free light chain ratio (0.26-1.65) and no presence of monoclonal protein via serum or urine immunofixation; **AND**
      2. Myocardial uptake of ^{99m}Tc-PYP demonstrated by >1.5 heart-to-contralateral ratio or grade ≥2 visual evidence; **OR**
      3. Documented presence of amyloid deposit by endomyocardial biopsy; **AND**
   E. Provider attestation of history of heart failure evidenced by prior hospitalization for heart failure or clinical evidence of heart failure (e.g., volume overload, elevated intracardiac pressures, heart failure symptoms requiring management with a diuretic); **AND**
   F. New York Heart Association (NYHA) functional class I-III; **AND**
   G. No prior history of liver or heart transplantation

II. Acoramidis (Attruby), tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are considered not medically necessary when used for all other conditions, including but not limited to:

A. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV

III. Acoramidis (Attruby), tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are 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 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 the patient has experienced a positive clinical response therapy (e.g., reduced cardiovascular hospitalizations, improved quality of life, slowing of disease progression, etc.); **AND**
IV. No prior history of liver or heart transplantation; **AND**
V. New York Heart Association (NYHA) functional class I-III; **AND**
VI. Medication will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e., inotersen (Tegsedi), patisiran (Onpattro) eplontersen (Wainua), acoramidis (Attruby), tafamidis meglumine (Vyndaqel), tafamidis (Vyndamax)].

Supporting Evidence

I. Acoramidis (Attruby), tafamidis meglumine (Vyndaqel), and tafamidis (Vyndamax) are transthyretin (TTR) stabilizers FDA approved for the treatment of cardiomyopathy (CM) of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.
II. Given the complexity of diagnosis and treatment of ATTR-CM, therapy should be prescribed by, or in consultation with, a cardiologist.
III. Transthyretin amyloid cardiomyopathy (ATTR-CM) is a restrictive heart disease caused by extracellular deposits of amyloid fibrils, clumps of misfolded TTR proteins which normally circulate through the body carrying retinol (vitamin A) and thyroxine. This condition results in heart failure, usually with a preserved ejection fraction, due to walls of the heart stiffening and preventing the heart from filling properly. Shortness of breath, arrhythmias, and death are all results of the disease. There are two types of ATTR-CM, hereditary (hATTR-CM), sometimes called variant, and wild type (wATTR-CM). Hereditary cases are due to a variant in the TTR gene, with symptoms presenting as early as the 30s, and more commonly affects African Americans in the United States with one in 25 Black individuals having the gene variant. Wild type does not include the gene mutation and makes up about 90% of all cases of ATTR-CM, and while it affects the heart, it can also cause carpal tunnel syndrome and peripheral neuropathy, mainly affecting elderly men regardless of any one race, with an average age of 74 years at diagnosis. Historically, considered a rare disease, advancements in cardiac imaging and better understanding of the TTR gene have led to 5,000-7,000 new cases identified per year. A

conservative estimate suggest that 50,000 to 150,000 adults in the US have ATTR-CM. Life expectancy for untreated patients with ATTR-CM is about two to five years after diagnosis.

IV. Cardiomyopathy (CM) of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) should be suspected in all elderly patients with recurrent HF exacerbations, irrespective of their ejection fraction status. Often, patients will present with fatigue, poor exercise tolerance, and shortness of breath with the New York Heart Association (NYHA) functional class I to III. In addition, patients may have significant right ventricular involvement, causing peripheral congestive symptoms like elevated jugular venous pressure, lower extremity edema, hepatic congestion, and ascites. Those with wATTR-CM additionally develop extracardiac symptoms due to nerve entrapment with amyloid deposits. Bilateral carpal tunnel syndrome and lumbar spinal stenosis are commonly associated with wATTR-CM and often occur five to ten years before a diagnosis of ATTR-CM occurs.

V. The cardiac amyloidosis diagnostic process begins with clinical history, electrocardiogram (ECG), and transthoracic echocardiogram. Echocardiographic clues can also rule out other causes of heart failure (HF), but it is not diagnostic to ATTR-CM alone. The 2022 American Heart Association notes that patients may undergo cardiovascular magnetic resonance (CMR) imaging which can further identify amyloidosis with sensitivity and specificity of 85 to 90%, but cannot distinguish between light chain amyloidosis heart failure (AL-CM) and ATTR-CM. If the above is consistent with cardiac amyloidosis, monoclonal protein tests are performed. Patients who test positive for serum/urine immunofixation electrophoresis (IFE) and have a serum kappa/lambda free light chain abnormality, should be further screened for AL-CM as treatment in conjunction with a hematologist should begin as soon as possible. If the protein test is negative, cardiac scintigraphy with technetium pyrophosphate (Tc-PYP) is preformed, with a positive test indicative of ATTR-CM. Once images are obtained, both semiquantitative and quantitative approaches are performed to evaluate uptake in the heart. The semiquantitative grading involves using the Perugini scale to compare heart-to-rib uptake: grade 0 is no cardiac and normal rib uptake; grade 1 is cardiac less than rib uptake; grade 2 is cardiac equal to rib uptake; and grade 3 is cardiac greater than rib uptake with mild/absent rib uptake. Quantitative analysis involves comparison of mean counts as determined by a region of interest placed over the heart and compared with a similar sized region of interest placed over the contralateral chest. In the absence of a light chain abnormality, the Tc-99m PYP scan is diagnostic of TTR-CA if there is grade 2 to 3 cardiac uptake or a heart/contralateral chest ratio >1.5. Patients may also elect to undergo genetic testing to see if positive for the gene variation due to high likelihood of familial inheritance of the gene mutation. A diagnostic pitfall would be to interpret a cardiac scintigraphy scan without a concomitant monoclonal protein screen; a scintigraphy scan alone is neither appropriate nor valid for distinguishing ATTR-CM from AL-CM. An endomyocardial biopsy with congo red staining, has a sensitivity and specificity of 100%, and remains the gold standard to diagnose ATTR-CM, but patients and physicians may prefer the other less invasive measures for confirmation such as scintigraphy.

VI. There are no guidelines specific to ATTR-CM in the U.S.; however, the American Heart Association (2022) and American College of Cardiology (2023) have recommendations for the treatment of hATTR-CM and wATTR-CM. Currently only the TTR stabilizer, tafamidis (Vyndamax/Vyndaqel) is noted as first line use in cardiomyopathy on top of standard of care HF medications (e.g. diuretics, beta-blockers) and anti-arrhythmics. The guidelines have not been updated to include acoramidis (Attruby). The guidelines do not comment on using other TTR agents in combination, such as TTR silencers with TTR stabilizers. Clinical trial programs for acoramidis (Attruby) and tafamidis (Vyndamax/Vyndaqel) did not study these medications in combination with TTR silencers, therefore such use would not be appropriate due to lack of

safety and efficacy data supporting such a treatment approach (i.e., in combination with inotersen (Tegsedi), patisiran (Onpattro), and/or eplontersen (Wainua)). Additionally, use of tafamidis (Vyndamax/Vyndaqel) in combination with acoramidis (Attruby) is not permitted as combination treatment is not expected to result in greater efficacy or better patient outcomes, as demonstrated in the ATTRibute-CM clinical trial.

tafamidis (Vyndamax/Vyndaqel)

I. 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). 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. Patients were excluded if they had NYHA Class IV heart failure, primary amyloidosis, or a history of liver or heart transplantation. Patients on average were 74 years of age, 90% male, with wild-type TTR (65%); they were randomized 1:2:2: to tafamidis 20mg, 80mg, or placebo once daily.

II. 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 NYHA class III patients, cardiovascular related hospitalizations were actually higher among patients receiving tafamidis meglumine (Vyndaqel) than those receiving placebo.

III. 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.

IV. 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.

V. Vyndamax (tafamidis) was developed for patient convenience. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) are not substitutable on a per-mg basis.

acoramidis (Attruby)

I. The safety and efficacy of acoramidis (Attruby) was studied in a Phase 3, randomized, double-blind, placebo-controlled study (ATTRibute-CM) that ran for 30 weeks. A total of 632 adult patients were randomized 2:1 to receive acoramidis (N=421) 800 mg twice daily or matching placebo (n=211) on top of standard heart failure medications (e.g., diuretics 93%, beta-blockers 57%). On average, patients were aged 77 years, White (87%), male (90%), with wild-type TTR (90%), and New York Heart Association (NYHA) class II (69.6%). Due to a protocol amendment post the approval of tafamidis (Vyndamax/Vyndaqel) patients were allowed to begin tafamidis (Vyndamax/Vyndaqel); 61 patients (15.9%) in the acoramidis (Attruby) arm and 46 in the placebo arm (22.8%) were on tafamidis (Vyndamax/Vyndaqel) plus the respected study arm agent. Patients were required to be on 12 months of single arm study agent before allowance of tafamidis (Vyndamax/Vyndaqel) and average exposure of tafamidis (Vyndamax/Vyndaqel) was 11 months. Patients with NYHA Class IV and chronic kidney disease (CKD) stage IV were excluded from the study. The primary endpoint was a four-step hierarchical test that included: death from any cause (which was defined in the trial as death from any cause, receipt of a heart transplant, or receipt of an implanted cardiac mechanical assist device), cumulative frequency of

cardiovascular-related hospitalization (CVH), the change from baseline in the N-terminal pro-B-type natriuretic peptide (NT-proBNP) level, and the change from baseline in the 6-minute walk distance in the modified intent to treat (mITT) population, those with an estimated glomerular filtration rate (eGFR) ≥30 ; analyzed using the Finkelstein-Schoenfeld Method of wins versus losses on matched pair tests.

II. The primary analysis met statistical significance in the percent number of wins versus placebo; 63.7 with acoramidis (Attruby) versus 35.9 with placebo, a win ratio of 1.8 (95% CI:1.4-2.2), p<0.001.
    - Furthermore, all cause-mortality (ACM) and cardiovascular related hospitalizations (CVH) sub-composite met statistical significance, with hazard ratio (HR) of 0.645 (95%CI: 0.500-0.832, p=0.0008). This indicates a 35% risk reduction for ACM and CVH associated with acoramidis (Attruby).
    - Additional individual components of the hierarchical composite that were statistically significant in favor of acoramidis (Attruby) versus placebo were reduction of CVH, improvement in NT-proBNP levels, and changes in 6MWD.
    - The ACM component by itself was not statistically significant in the modified intention to treat (mITT) population, with 19.3% versus 25.7% of patients achieving this endpoint in the acoramidis (Attruby) vs placebo arm and a relative risk reduction (RRR) of 25% in favor of acoramidis (Attruby) p=0.057. However, ACM evaluated in the intention to treat (ITT) population (prespecified secondary endpoint) which included patients with eGFR of 15-30, was statistically significant, with 20.0% of patients in the acoramidis (Attruby) arm reaching this endpoint versus placebo at 27.0%, p=0.039.
    - Secondary outcomes included health-related quality of life assessment utilizing the KCCQ-OS questionnaire. The results was -11.48 in the acoramidis (Attruby) arm versus -21.42 in placebo, difference of 9.94 [5.19-14.10] p<0.0001.
    - Sensitivity analyses indicated that receiving tafamidis (Vyndamax/Vyndaqel) with acoramidis (Attruby) showed no additional benefit.

III. Upon completion of ATTRibute-CM, 389 patients enrolled in the open-label extension study. Continuous use of acoramidis (Attruby) was associated with sustained clinical benefits at month 42, with HR for all-cause mortality of 0.64.

IV. The overall quality of evidence for acoramidis (Attruby) is considered moderate. ATTRibute-CM demonstrated statistically significant and clinically meaningful benefits in favor of acoramidis (Attruby) when evaluating the primary endpoint (composite) and select hierarchical components. Most importantly, all-cause mortality (ITT population only) and cardiovascular related hospitalizations risk was reduced with acoramidis (Attruby) treatment by 35%. While all-cause mortality alone was not statistically significant at the end of 30 months in the modified intent to treat group, this may be due to the relative short-term study time frame and a healthier overall population at baseline. Real world applications to excluded populations, such as those with NYHA class IV symptoms, are unknown at this time.

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 both the ATTR-ACT trial and ATTRibute-CM 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 and acoramidis

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) and acoramidis (Attruby) 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 approval.

III. Primary (light chain) amyloidosis
    A. In both pivotal trials, 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)/Vyndaqel (tafamidis megluime) [prescribing information]. New York, NY: Pfizer Labs; May 2019. Updated 10/2023.
2. Buxbaum J. Oligonucleotide Drugs for Transthyretin Amyloidosis. NEJM. 2018;379(1):82-85. doi:10.1056/NEJMe1805499.
3. 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
4. Coelho T, Ericzon B, Falk R, et al. A Guide to Transthyretin Amyloidosis. Available at: http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf.
5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. FDA Issues Complete Response Letter For Pfizer's Tafamidis Meglumine New Drug Application [press release]. Pfizer Inc, June 18, 2012
11. 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.
12. AL Amyloidosis. Amyloidosis Foundation website. Available at: www.amyloidosis.org/facts/al/#faqs
13. Vyndaqel (tafamidis meglumine) AMCP Dossier. New York, NY: Pfizer Labs May 24, 2019
14. Gillmore JD, Judge DP, Cappelli F, et al. Efficacy and Safety of Acoramidis in Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2024;390(2):132-142. doi:10.1056/NEJMoa2305434
15. Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2023;81:1076-1126.
16. Kittleson MM, Maurer MS, Ambardekar AV, et al. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association [published correction appears in Circulation. 2021 Jul 6;144(1):e10. doi: 10.1161/CIR.0000000000000997]

17. Jain A, Zahra F. Transthyretin Amyloid Cardiomyopathy (ATTR-CM) [Updated 2023 Apr 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574531/
18. Judge, Daniel P., Alexander, Kevin M., Cappelli, Francesco. "Acoramidis Improves Clinical Outcomes in Patients With Transthyretin Amyloid Cardiomyopathy: Post Hoc Recurrent Event Analyses of ATTRibute-CM" Poster presented at 2024 HEART FAILURE SOCIETY OF AMERICA ANNUAL SCIENTIFIC MEETING, SEPTEMBER 27-30; ATLANTA, GA, USA

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
eplontersen (Wainua)	Hereditary transthyretin-mediated amyloidosis with polyneuropathy
inotersen (Tegsedi)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated the serum kappa/lambda free light chain ratio to be within normal range and added criteria to include grade 2/3 uptake or >1.5 heart-to-contralateral ratio for myocardial uptake on scintigraphy. Updated supporting evidence.	10/2025
Reformatting to align with new policy format. Addition of acoramidis (Attruby) for indication of ATTR-CM. Expansion of heart failure definition in initial criteria. Addition of monoclonal protein screening to initial criteria. Updates to supportive evidence section.	02/2025
Policy created	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP087

Description

Apomorphine (Apokyn, Kynmobi), a non-ergoline dopamine agonist, is administered as a subcutaneous injection. It possesses an unknown mechanism in the treatment of Parkinson's disease but is suggested that its effects are attributed to stimulation of post-synaptic D(2)-type receptors within the brain.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
apomorphine (Apokyn)	10 mg/mL subcutaneous injection	Parkinson's Disease	54 mL/30 days
apomorphine (Kynmobi)	10 mg sublingual film	Parkinson's Disease	150 films/30 days
	15 mg sublingual film		150 films/30 days
	20 mg sublingual film		150 films/30 days
	25 mg sublingual film		150 films/30 days
	30 mg sublingual film		150 films/30 days
	10/15/20/25/30 mg titration kit		1 kit/30 days
apomorphine (Onapgo)	4.9 mg/mL subcutaneous injection	Parkinson's Disease	600 mL/30 days

Initial Evaluation

I. **Apomorphine (Apokyn, Kynmobi, Onapgo)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Must be prescribed by, or in consultation with, a neurologist; **AND**
   C. Not used in combination with a 5-HT_3 receptor antagonist (e.g. ondansetron, granisetron, dolasetron, etc.); **AND**
   D. A diagnosis of **Parkinson's disease** when the following are met:
      1. Member experiences predictable acute, intermittent hypomobility "off" episodes; **AND**
      2. Provider must attest that the first dose will be done in office and the member will be monitored; **AND**
      3. Member will be taking carbidopa/levodopa concurrently with apomorphine (Apokyn, Kynmobi, Onapgo); **AND**
      4. Treatment with ONE of the following has been ineffective, contraindicated, or not tolerated:
         i. Dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)

ii. Monoamine oxide-B (MAO-B) inhibitor (e.g. selegiline, rasagiline)
iii. Catechol-O-methyl transferase (COMT) inhibitors (e.g. entacapone, tolcapone)

II. Apomorphine (Apokyn) is considered investigational when used for all other conditions, including but not limited to:
A. Erectile dysfunction

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 demonstrated benefit through reduction of "off" episodes/hypomobility

Supporting Evidence

I. Apomorphine subcutaneous injection (Apokyn) was studied in three randomized controlled trials. All patients in the studies were on L-dopa, 86% of patients were on oral dopaminergic agonists, 31% were on catechol-ortho-methyl transferase inhibitors, and 10% were on monoamine B oxidase inhibitors.
- Study one was a randomized, double-blind, placebo-controlled, parallel-group trial evaluating 29 patients with advanced Parkinson's disease who had at least two hours of "off" time per day. Apomorphine (Apokyn) demonstrated a statistically significant decrease in the Unified Parkinson's Disease Rating Scale (UPDRS) compared to placebo, with a mean change from baseline of -23.9 and -0.1 (p<0.001) respectively.
- Study two was a randomized, placebo-controlled crossover trial evaluating 17 patients with Parkinson's disease who had been using apomorphine (Apokyn) for at least three months. Apomorphine (Apokyn) demonstrated a statistically significant decrease in UPDRS compared to placebo, with a mean change from baseline of -20 and -3 respectively.
- Study three was a randomized, double-blind, placebo-controlled, trial evaluating 62 patients with Parkinson's disease who had been using apomorphine (Apokyn) for at least three months. Apomorphine (Apokyn) demonstrated a statistically significant decrease in UPDRS at 20 minutes compared to placebo, with a mean change from baseline of -24.2 vs -7.4 (p<0.0001) respectively.

II. Apomorphine sublingual tablet (Kynmobi) was studied in one phase 3 clinical trial that consisted of an open label dose-titration phase followed by a 12 week randomized, double-blind, placebo-controlled trial in 109 patients who had diagnosis of Parkinson's Disease and had at least two hours of 'off' time per day with predictable morning 'off' periods. Patients continued concomitant Parkinson's Disease medications including levodopa-containing agents (100% apomorphine and placebo group), dopamine agonists (56% apomorphine and placebo group), monoamine oxidase-B inhibitors (41% apomorphine, 44% placebo), amantadine (15%

apomorphine, 29% placebo) and catechol-O-methyltransferase inhibitors (9% apomorphine and placebo groups).

- The primary efficacy endpoint, mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS Part 3 score at week 12, was significantly greater in the apomorphine group compared to placebo (change -11.1, SE 1.46, 95% CI -14.0 to -8.2, with apomorphine sublingual film VS -3.5, 1.29, -6.1 to -0.9, with placebo) with a least squares mean difference of -7.6 (SE 1.96, 95% CI -11.5 to -3.7; p=0.0002).
- The key secondary endpoint, percentage of patients with a self-rated full on response within 30 minutes at the 12-week visit, was significantly greater in the apomorphine group (35%, SE 21 to 35) compared to placebo (16%, SE 8 to 30) (OR 2.81, 1.04 to 7.64; p=0.043).

III. Use of apomorphine (Apokyn, Kynmobi) with 5-HT_3 antagonists (e.g. ondansetron, granisetron, dolasetron, or alosetron) is contraindicated. There have been reports of profound hypotension and loss of consciousness when administered together.

IV. Adverse events are similar between both the sublingual and subcutaneous formulations of apomorphine (Apokyn, Kynmobi), including syncope, hypotension, orthostatic hypotension, nausea, vomiting, falling asleep during activities of daily living, somnolence, and hallucinations or psychotic-like behavior. Oral mucosal irritation was common during the clinical trials for apomorphine sublingual films (Kynmobi) with approximately 20% of patients developing mild to moderate oral mucosal ulcerations or stomatitis, oral soft tissue pain or paresthesia, oral/pharyngeal soft tissue swelling or oral mucosal erythema.

V. Because of the high incidence of nausea and vomiting with apomorphine (Apokyn, Kynmobi) at recommended doses, a non 5HT-3 antagonist antiemetic (e.g. trimethobenzamide) should be initiated beginning three days prior to starting apomorphine (Apokyn, Kynmobi). Treatment with the antiemetic should be continued only as long as necessary to control nausea and vomiting symptoms, and ideally is discontinued no longer than two months after initiation of apomorphine (Apokyn, Kynmobi).

VI. Due to high incidence of syncope/hypotension/orthostatic hypotension with apomorphine (Apokyn, Kynmobi), dose initiation should occur under the supervision of a healthcare provider where blood pressure and pulse can be monitored according to the package insert.

VII. According to the prescribing information for apomorphine subcutaneous injection (Apokyn), there is no evidence from controlled trials that doses greater than 0.6mL (6mg) gave an increased effect and therefore, individual doses exceeding 0.6mL (6mg) are not recommended. The average frequency of dosing in the developmental program is 3 times per day. Additionally, there is limited experience with single doses greater than 0.6 mL (6mg), dosing more than five times per day, and with total daily doses greater than 2mL (20mg).

VIII. According to the prescribing information for apomorphine sublingual tablets (Kynmobi), the dose range is 10mg to 30mg per dose. The maximum single dose should not exceed 30mg; do not administer more than five doses per day.

Investigational or Not Medically Necessary Uses

I. Apomorphine (Apokyn) has not been adequately studied in patients with erectile dysfunction.

References

1. Apokyn [prescribing information]. USWorldMeds: Louisville, KY; November 2019.
2. Pfeiffer RF, Gutmann L, Hull KL, Bottini PB, Sherry JH. Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. Parkinsonism Relat Disord. 2007;13(2):93-100.
3. Dewey RB, Hutton JT, Lewitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. Arch Neurol. 2001;58(9):1385-92.
4. Uptodate, Inc. Medical management of motor fluctuations and dyskinesia in Parkinson disease [database online]. Waltham, MA. Updated 09/16/19. Available at: http://www.uptodate.com/home/index.html. [Accessed 11/04/19]
5. Orlanow CW et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomized, double-blind, placebo-controlled phase 3 study. *Lancet Neurol* 2020; 19:135-44.
6. Kynmobi [prescribing information]. Sunovion Pharmaceuticals, Inc.: Marlborough, MA; May 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Onapgo to the policy	03/2025
• Added apomorphine sublingual films (Kynmobi) to policy • Added requirement of member is experiencing predictable acute, intermittent hypomobility "off" episodes • Updated renewal criteria to require prior approval through this OR prior health plan (not established via samples) • Removed renal criteria requirement confirming lack of toxicity to therapy • Updated apomorphine subcutaneous injection (Apokyn) QLL to align with FDA label and package size of 3mL/cartridge	03/2021
Criteria transitioned to policy	10/2019
Previous reviews	11/2014 12/2008 09/2008
Criteria created	09/2005

aprocitentan (Tryvio™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP299

Description

Aprocitentan (Tryvio) is an orally administered endothelin receptor antagonist.

Length of Authorization

- Initial: Length of Benefit
- Renewal: Lenth of Benefit

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
aprocitentan (Tryvio)	Resistant hypertension	12.5 mg tablets	30 tablets/30 days*

**Quantity exceptions exceeding quantity limit are not allowed*

Initial Evaluation

I. **Aprocitentan (Tryvio)** 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 or hypertension specialist; **AND**
   C. A diagnosis of **resistant hypertension** when the following are met:
      1. Provider attestation that the member's blood pressure remains above target goal despite appropriate adherence to standard of care therapies; **AND**
      2. Provider attestation that secondary causes of hypertension have been ruled out (i.e. pseudo-resistant hypertension, white coat hypertension); **AND**
      3. Treatment with at least one agent in all of the following groups has been ineffective or not tolerated, or all are contraindicated:
         i. Group 1: renin-angiotensin system (RAS) inhibitors (e.g., losartan, valsartan, lisinopril, enalapril)
         ii. Group 2: calcium channel blockers (CCB) (e.g., amlodipine, felodipine, nifedipine, verapamil, diltiazem)
         iii. Group 3: thiazide/thiazide-like diuretics (e.g., hydrochlorothiazide, chlorthalidone, indapamide); **AND**
         iv. Group 4: mineralocorticoid receptor antagonist (e.g., spironolactone, eplerenone); **AND**
      4. Treatment with an additional antihypertensive agent of a different mechanism of action (e.g., beta blockers [e.g., bisoprolol, atenolol, metoprolol], hydralazine, clonidine, etc.) has been ineffective, not tolerated, or all are contraindicated; **AND**
      5. Background blood pressure therapies will be continued along with aprocitentan (Tryvio), unless contraindicated or not tolerated.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

II. Aprocitentan (Tryvio) is considered investigational when used for all other conditions, including but not limited to:
    A. Pulmonary hypertension

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., reduced blood pressure) **AND**
IV. Background blood pressure therapies will be continued along with aprocitentan (Tryvio), unless contraindicated or not tolerated.

Supporting Evidence

I. Aprocitentan (Tryvio) was studied in a multicenter, blinded, randomized, parallel-group Phase 3 trial (PRECISION). The main portion of the trial included a 4-week, double-blind, randomized treatment of aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo (part 1), followed by a single (patient)-blind, active treatment portion for 32 weeks where all participants received aprocitentan 25 mg (part 2), and concluded with a 12-week, double-blind, re-randomized withdrawal phase to either aprocitentan 25 mg or placebo (part 3).
II. The primary outcome was the change of sitting office systolic BP (SBP) from baseline to week 4 and the key secondary outcome was change of sitting office SBP from withdrawal baseline (week 36) to week 40. The primary outcome was met with a decrease in SBP by -15.3 mmHg and -11.5 mmHg for aprocitentan 12.5mg and placebo, respectively (difference of -3.8 mmHg [97.5% CI, -6.8 to -0.8; p=0.0042].
III. Although the change in SBP from baseline was found to be numerically larger and statistically significant, the difference in mean change of aprocitentan (Tryvio) compared to placebo is not considered to be clinically meaningful. Additionally, sustained reduction at the FDA approved dose (12.5mg) is questionable as readable data for this dose is limited to 4 weeks post-initiation, limiting the confidence in the clinical benefit in the FDA-approved population. Therefore, due to the lack of clinically meaningful benefit compared to placebo and limited data to support long-term efficacy of the FDA-approved dose in a chronic disease state, the overall quality of evidence is low.
IV. Edema or fluid retention was the most reported adverse event during the trial in the aprocitentan groups, with most cases considered mild to moderate in severity, and found to be dose dependent. The incidence rates were 9.1% vs. 2.1% for the 12.5mg and placebo, respectively. This adverse event occurred most frequently in patients with CKD. One other side effect of note was anemia at 3.7% vs. 0% between the 12.5mg tablet and placebo, respectively. There was a total of 13 deaths reported, 11 of which were considered treatment emergent and ultimately were ruled as not being related to the study drug. Five deaths were CV-related and primarily occurred in the 25mg arm. There were no documented deaths in the 12.5mg group.

V. The 25mg is not FDA approved as it did not demonstrate a meaningful improvement in blood pressure reduction when compared to the 12.5 mg dose and there was an increase in ADEs especially edema and fluid retention. For this reason, quantity exceptions to allow for a quantity above 12.5 mg are not allowed.

VI. The 2017 High Blood Pressure Guidelines from American College of Cardiology /American Heart Association (ACC/AHA) define resistant hypertension as not achieving blood pressure (BP) control despite taking three or more agents with complementary mechanisms of action (MOAs) or achieving BP control but requiring at least four medications to do so. Their treatment recommendations for resistant hypertension include a triple-therapy regimen consisting of a thiazide diuretic, calcium channel blocker (CCB), and an angiotensin converting enzyme inhibitor (ACE-I) OR angiotensin receptor blocker (ARB). Guidelines recommend addition of spironolactone (or other agent with a complementary or a different mechanism if intolerable) if BP goal is not achieved despite proper adherence on triple-therapy regimen.

VII. The European Society for Hypertension (ESH) 2023 guidelines defines resistant hypertension as failure to lower BP to <140/90 mmHg despite appropriate lifestyle measures and maximized dose with at least three or more medications. Their recommendations for resistant hypertension treatment includes maximizing a triple-therapy regimen that should include an ACE-I OR ARB, a CCB, and a thiazide diuretic. If not controlled, then other agents with other MOAs can be included, preferring spironolactone (if not contraindicated). Other agents that could be added instead are beta-blockers, alpha blockers, or centrally acting agents.

References

1. Tryvio. Package Insert. Idorsia Pharma; March 2024.
2. Food and Drug Administration. NDA Approval letter, March 2024. Accessed March 2024. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2024/217686Orig1s000ltr.pdf
3. Schlaich MP, Bellet M, Weber MA, et al. Dual endothelin antagonist aprocitentan for resistant hypertension (PRECISION): a multicentre, blinded, randomised, parallel-group, phase 3 trial [published correction appears in Lancet. 2023 Jan 28;401(10373):268]. *Lancet*. 2022;400(10367):1927-1937. doi:10.1016/S0140-6736(22)02034-7
4. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Hypertension. 2018 Jun;71(6):e140-e144]. *Hypertension*. 2018;71(6):e13-e115. doi:10.1161/HYP.0000000000000065
5. Mancia G, Kreutz R, Brunstrom M, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). Journal of Hypertension 41(12):p 1874-2071, December 2023. | DOI: 10.1097/HJH.0000000000003480

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP318

Description

Arimoclomol (Miplyffa) is a synthetic pyridine derivative that is not currently identified within a specific drug class. Levacetylleucine (Aqneursa) is a is a modified amino acid (N-acetyl-L-leucine; NALL) that uses monocarboxylate transporters to cross the blood-brain barrier and reach the central nervous system.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
arimoclomol (Miplyffa)	Treat neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older	47 mg capsule	90 capsules/30 days
		62 mg capsule	
		93 mg capsule	
		124 mg capsule	
levacetylleucine (Aqneursa)	Treat neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients weighing ≥15 kg	1 g unit dose packet	112 unit-dose packets/28 days

Initial Evaluation

I. **Arimoclomol (Miplyffa) or levacetylleucine (Aqneursa)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a neurologist, endocrinologist, metabolic disorder specialist, or a physician specializing in the treatment of Niemann-Pick disease type C; **AND**
   B. Member has a diagnosis of **Niemann-Pick disease type C (NPC)** when the following are met:
      1. Presence of a genetically confirmed mutation in both alleles of NPC1 or NPC2; **OR**
         i. Mutation in only one allele of NPC1 or NPC2 plus either positive filipin staining or elevated cholestane-triol/oxysterols level (i.e., greater than two times the upper limit of normal); **AND**
      2. Member has one or more neurological symptom(s) of Niemann-Pick disease type C (e.g., loss of motor function, difficulty swallowing, speech and cognitive impairment, etc.); **AND**
      3. Member can walk independently or with assistance; **AND**
   C. The request is for:
      1. Levacetylleucine (Aqneursa); **AND**
         i. Member is 4 years of age or older; **AND**
         ii. Member weighs 15 kg or more; **AND**

iii. Levacetylleucine (Aqneursa) will not be used in combination with arimoclomol (Miplyffa); **OR**

2. Arimoclomol (Miplyffa); **AND**
   i. Member is 2 years of age or older; **AND**
   ii. Member weighs 8 kg or more; **AND**
   iii. The medication will be taken in combination with miglustat*; **AND**
   iv. Arimoclomol (Miplyffa) will not be used in combination with levacetylleucine (Aqneursa)

*Please note: medications notated with an asterisk may require additional review.

II. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) are considered investigational or not medically necessary when used for all other conditions, including but not limited to:
   A. Amyotrophic Lateral Sclerosis
   B. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) used in combination with each other for any indication, including Niemann-Pick disease type C (NPC)
   C. Gaucher Disease
   D. Myositis

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's weight is documented; **AND**
IV. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) will not be used in combination with each other; **AND**
V. Member has experienced benefit from treatment defined as disease stabilization or slowed disease progression and treatment provides clinical benefit to the member (e.g., improvement in gait, sitting, stance, speech, fine motor skills, etc.); **AND**
VI. If the request is for arimoclomol (Miplyffa), arimoclomol (Miplyffa) will be used in combination with miglustat*

*Please note: medications notated with an asterisk may require additional review.

Supporting Evidence

I. Niemann-Pick disease type C (NPC) is a rare, inherited lysosomal storage disorder characterized by the abnormal accumulation of cholesterol and other lipids in the cells. These genetic mutations impair the intracellular trafficking of lipids, leading to progressive neurological and hepatic dysfunction. Biomarker profile genetic testing identifying two alleles with known disease-causing mutations in either NPC1 or NPC2 gene confirms the diagnosis of NPC, and is the most reliable way to confirm the diagnosis of NPC. As a neurodegenerative disease with a very heterogeneous presentation, symptoms typically appear in childhood and can include developmental delay, ataxia, seizures, and progressive liver enlargement, with later stages often involving cognitive decline, motor impairment, and difficulty swallowing. The age of onset of

neurological symptoms predicts the severity of the disease and determines life expectancy. The prevalence of NPC is estimated to be approximately 1 in 100,000 to 150,000 live births, and it is estimated that there are 900 people in the United States with NPC. The spectrum of NPC ranges from a neonatal rapidly progressive fatal disorder to an adult-onset chronic neurodegenerative disease. The late-infantile and juvenile-onset forms account for the majority of NPC cases. Across all phenotypes, the median age of death is 13 years (range, 0.1 to 69 years), most often due to respiratory failure.

II. Therapeutic management of NPC primarily focuses on symptom management and slowing disease progression, as there is no cure. Supportive therapies, such as physical and occupational therapy, anti-seizure medications, and interventions to manage liver complications, are often recommended to address specific symptoms. Early diagnosis and intervention are crucial for improving the quality of life and prolonging survival, but the overall prognosis remains poor, particularly in later stages of the disease. Regular monitoring and a multidisciplinary care approach are essential to optimize treatment and manage complications.

III. Miglustat (Opfolda, Yargesa, Zavesca) has been approved in the European Union, Canada, and Japan and is considered a standard of care for treating progressive neurological complications in NPC internationally. Niemann-Pick Type C Guidelines Working Group and the International Niemann-Pick Disease Alliance 2018 consensus clinical management recommend miglustat as an effective and recommended treatment option in the management of existing neurologic manifestations of NPC in children and adults who exhibit symptoms of neurological decline (Strength of recommendation: 2; Level of evidence: C). Clinical evidence suggests that miglustat can help slow the progression of the disease particularly in patients with moderate symptoms or in the early stages of the disease, with effects noted on motor and cognitive functions. Data from a randomized, controlled trial and a retrospective, observational cohort study support the use of miglustat in the treatment of NPC disease in adults and children 12 years and older. Administered orally, miglustat's dosage depends on the patient's age and weight, with treatment often beginning in early childhood for those with signs of neurological involvement. However, common side effects, including gastrointestinal issues such as diarrhea, nausea, and weight loss require careful monitoring. Dose adjustments are often necessary to manage these side effects. Despite miglustat's position as a standard of care, there has been no significant change in the survival of patients with NPC.

IV. From the 2018 International NPC guidelines, "miglustat therapy is not appropriate for patients who have profound neurological disease, which, in the opinion of the attending physician, would make it difficult to assess for any improvements with therapy. Such symptoms may include but are not limited to:

    a. Profound dementia resulting in the need for 24 h care
    b. Inability to ambulate without a wheelchair
    c. Complete lack of verbal communication
    d. Swallowing difficulties profound enough to require tube feeding through a per-cutaneous gastrostomy..."

Additionally, the guidelines do not recommend miglustat therapy in the following situations: patients who are pre-symptomatic or only have spleen/liver enlargement, patients with another life-threatening illness with estimated life span less than 1 year (Strength of recommendation: 2; Level of evidence: C).

Arimoclomol (Miplyffa)

V. As of September 2024, there are two FDA-approved therapies for NPC: arimoclomol (Miplyffa) and levacetylleucine (Aqneursa). Arimoclomol (Miplyffa) is an orally administered capsule that is

indicated for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients two years of age and older and weigh ≥8kg. The approval of arimoclomol (Miplyffa) was based on data from a Phase 3, randomized, double-blind, placebo-controlled, 12-month trial in patients aged two to 18 years with NPC1 or NPC2. Fifty patients were randomized 2:1 to treatment with weight-adjusted arimoclomol (Miplyffa) (31 to 124 mg) or placebo orally three times per day. Inclusion criteria included participants with at least one neurological sign of NPC, ability to walk independently or with assistance, and on stable dose of miglustat for at least 6 continuous months. Among these 50 patients, 39 (78%) received miglustat as background treatment in the trial. The primary endpoint evaluated a rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score in the patients who used miglustat as their background treatment at 12 months. The R4DNPCCSS is a measure of NPC disease progression that looks at four items that patients with NPC, their caregivers and physicians have identified as most relevant including ambulation, speech, swallow and fine motor skills. Higher scores signify a greater severity of the disease. A 0.2-point decrease on the R4DNPCCSS was observed in patients who received arimoclomol (Miplyffa) in combination with miglustat, compared with an increase of 1.9 points in patients who received placebo with miglustat. Secondary endpoints (change from baseline in CGI-I, R4DNPCCSS, 17-domain NPCCSS, NPC-cdb, EQ-5D-y, 9HPT, SARA) were assessed and found to be not statistically significant. While the primary outcome was assessed via a validated assessment tool, the quality of evidence is considered low as there are several uncertainties that remain including lack of additional well-designed confirmatory trials, lack of a well-established MOA, unknown effectiveness without miglustat, and a small population size that could impact the interpretability of the rescored R4NPCCSS which limit the durability of results. Although arimoclomol (Miplyffa) showed a statistically significant difference in the modified R4DNPCCSS score, the effect of treatment was relatively small. The most common adverse reactions in arimoclomol (Miplyffa)-treated patients (≥15%) were upper respiratory tract infection, diarrhea, and decreased weight. Serious adverse reactions reported in arimoclomol (Miplyffa)-treated patients were three hypersensitivity reactions including urticaria and angioedema. Three (6%) of the arimoclomol (Miplyffa)-treated patients had the following adverse reactions that led to withdrawal: increased serum creatinine (one patient), and progressive urticaria and angioedema (two patients). One patient in the arimoclomol group died, assessed as related to NPC progression. There are no specific contraindications to using arimoclomol (Miplyffa); however, warnings and precautions include: hypersensitivity reactions, embryofetal toxicity, and increase creatinine.

VI. Arimoclomol (Miplyffa) is administered orally three times daily, with or without food, and is dosed based on patient body weight (see appendix for dosing). Arimoclomol (Miplyffa) must be administered with miglustat. There are limited data to determine the efficacy of arimoclomol (Miplyffa) without miglustat at this time.

Levacetylleucine (Aqneursa)

VII. Levacetylleucine (Aqneursa) is available as orally dosed unit packets given three times daily to treat neurological manifestations of NPC in adults and pediatric patients weighing ≥15 kg. The approval of levacetylleucine (Aqneursa) was based on data from a Phase 3, randomized, double-blind, placebo-controlled, two-period crossover study, which evaluated 12 weeks of levacetylleucine (Aqneursa) therapy in two groups. Patients were randomized in a 1:1 ratio to one of the two treatment sequences:

- Treatment Sequence 1 (N=30): levacetylleucine (Aqneursa) in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II
- Treatment Sequence 2 (N=30): placebo in Treatment Period I, followed by immediate crossover to levacetylleucine (Aqneursa) in Treatment Period II

Most participants continued to receive background miglustat throughout the trial. Although the FDA label does not mandate the concurrent administration of miglustat with levacetylleucine (Aqneursa), it is probable that healthcare providers will choose to continue miglustat therapy when prescribing levacetylleucine (Aqneursa) as a majority of participants in the pivotal clinical trial were on concomitant miglustat (85%). Key inclusion criteria included patients aged four years or older, weighing >15kg, with a confirmed diagnosis of NPC, and at least mild disease-related neurological symptoms (SARA score between 7 – 34). The primary outcome was the functional Scale for the Assessment and Rating of Ataxia (fSARA). The estimated mean fSARA total score was 5.1 when patients were treated with Aqneursa and 5.6 when treated with placebo with an estimated treatment difference for the fSARA total score at −0.4 (95% CI (−0.7, −0.2); p<0.001). Most common adverse reactions (incidence ≥5%) in levacetylleucine (Aqneursa)-treated patients were abdominal pain, dysphagia, upper respiratory tract infections, and vomiting. Three patients had transient adverse events that were judged to be related to treatment (anal incontinence, restless-leg, rosacea). No serious adverse events occurred that were considered by an investigator to be related to levacetylleucine (Aqneursa) or placebo. One death was due to aspiration pneumonia after a preplanned placement of a percutaneous endoscopic gastrostomy tube and therefore was not related to trial treatment. There are no specific contraindications, but embryo-fetal toxicity is listed as a warning and precaution to using levacetylleucine (Aqneursa).

VIII. Although levacetylleucine (Aqneursa) showed a statistically significant difference in fSARA score, the clinical significance of these results are of low confidence. Considering NPC is a neurodegenerative disease with a very heterogeneous presentation, the short trial duration is a limitation of the study as a 12-week duration may not have been enough to be able to demonstrate benefit in a patient who is not progressing quickly and may explain why the treatment effect was small, albeit statistically significant. While the observed average treatment effect in fSARA is -0.45, at least a 1-point improvement in any of the four fSARA domains were seen more often when subjects received levacetylleucine (Aqneursa) than received placebo. As improvements in neurological symptoms would not be expected given the known natural history of NPC, this change is considered to be clinically meaningful. Furthermore, the two treatment sequences had significantly different baseline fSARA scores and the primary outcome analysis averaged the levacetylleucine (Aqneursa) response in each sequence. Extended follow-up data up to 12 months was presented at the European Academy of Neurology Congress in 2024 that evaluated 54 patients on levacetylleucine (Aqneursa). At 12 months, the mean change from baseline on the 5-domain Niemann-Pick disease type C Clinical Severity Scale (NPCCSS) was −0.115 in the levacetylleucine (Aqneursa) arm and 1.5 ± 3.1 in the historical cohort (mean difference 1.56; 95% CI, 0.31–2.92; P < 0.017). Given the limited data available, it is difficult to reliably determine whether there was a further decrease in fSARA as time on therapy increased. Longer-term data will help to ascertain treatment benefits.

IX. Due to differences in trial design, a formal cross-trial comparison of the pivotal trials for levacetylleucine (Aqneursa) and arimoclomol (Miplyffa) is not possible. Both treatments are

backed by a single small, relatively short randomized clinical trial, with each demonstrating a statistically significant but modest difference in the primary outcome. However, even a 1- to 2-point difference on each scale can lead to a meaningful improvement in a patient's quality of life.

Investigational or Not Medically Necessary Uses

I. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Amyotrophic Lateral Sclerosis
   B. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) used in combination with each other for any indication, including Niemann-Pick disease type C (NPC)
      i. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) have distinct mechanisms of action, although the exact ways in which they produce clinical effects in NPC are not fully understood. Sequential or combined use of Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) has not been studied in clinical trials, there is currently no evidence to support a synergistic effect, additive benefits, or assess safety when arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) are used combination.
   C. Gaucher Disease
   D. Myositis

Appendix

I. Arimoclomol (Miplyffa) dosing recommendation

Table 1. Recommended Dosage of Arimoclomol (Miplyffa) Based on Body Weight (kg)	
Patient Body Weight	Recommended Dosage
8 - 15 kg	47 mg three times a day
>15 - 30 kg	62 mg three times a day
>30 - 55 kg	93 mg three times a day
>55 kg	124 mg three times a day

   a. Miplyffa capsules may be swallowed whole or the contents of the capsule can be added to a suitable beverage, soft food, or added to water to allow administration via a feeding tube
   b. For patients with an eGFR 15 to < 50 mL/minute, the recommended oral dosage of arimoclomol (Miplyffa) in combination with miglustat is based on actual body weight and given twice daily.

II. Levacetylleucine (Aqneursa) recommended dosage: supplied in unit dose packets, each containing 1 g of levacetylleucine as granules for oral suspension

Table 2. Recommended Dosage of Levacetylleucine Based on Body Weight (kg)				
Body Weight (kg)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose
15 to <25 kg	1g	No dose	1g	2g
25 to <35 kg	1g	1g	1g	3g
35 kg or more	2g	1g	1g	4g

   a. Aqneursa packets can be added to water, orange juice, or almond milk. Contents can be administered via gastronomy tube (G-tube) by mixing with water.

III. While not FDA-approved, miglustat dosing is based on the doses studied in clinical trials/compendia and dose approved in the European Union for NPC. Miglustat use requires careful monitoring for side effects and regular treatment adjustments to optimize patient outcomes. Some forms of miglustat (Opfolda) are available in 65-mg capsules, therefore certain treatment regimens may not allow for exact dosing. *Please refer to updated clinical compendia for dosing recommendations. Generic miglustat along with brand (Opfolda, Yargesa, Zavesca) may require additional clinical review and prior authorization criteria to be met.*

Table 3. Off-label dosing for miglustat based on clinical compendia		
Patient population	BSA	Miglustat dose
<12 years of age	BSA ≤0.47 m^2	100 mg once daily
	BSA >0.47 to 0.73 m^2	100 mg 2 times daily
	BSA >0.73 to 0.88 m^2	100 mg 3 times daily
	BSA >0.88 to 1.25 m^2	200 mg 2 times daily
	BSA >1.25 m^2	200 mg 3 times daily
≥12 years of age and older	-	200 mg 3 times daily

IV. BSA (m^2) = $\sqrt{\frac{\text{height (cm) x weight (kg)}}{3600}}$

References

1. MIPLYFFA. Package Insert. Zevra Therapeutics; September 2024.
2. AQNEURSA. Package Insert. IntraBio Inc.; September 2024.
3. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. *Orphanet J Rare Dis*. 2018;13(1):50.
4. Burton BK, et al. Estimating the prevalence of Niemann-Pick disease type C (NPC) in the United States. *Mol Genet Metab.* 2021;134(1-2):182–187.
5. Cortina-Borja M, et al. Annual severity increment score as a tool for stratifying patients with Niemann-Pick disease type C and for recruitment to clinical trials. *Orphanet J Rare Dis*. 2018;13(1):143.
6. Mengel E, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: results from a double-blind, randomized, placebo-controlled, multinational phase 2/3 trial of a novel treatment. *J Inheri Metab Dis.* 2021;44(6):1463–1480.
7. Patterson MC, et al. Validation of the 5-domain Niemann-Pick type C clinical severity scale. *Orphanet J Rare Dis.* 2021;16(79):1–9.
8. Bremova-Ertl T, Ramaswami U, Brands M, et al. Trial of N -Acetyl- l -Leucine in Niemann–Pick Disease Type C. *N Engl J Med.* 2024;390(5):421-431.
9. Martakis K, et al. Long-term findings of N-acetyl-L-leucine for Niemann-Pick disease type C. *Neuropediatrics*. 2024;55(S01):S1–S25.

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
miglustat (Opfolda, Yargesa, Zavesca) and eliglustat (Cerdelga) Policy	Niemann-Pick disease type C *(off-label)*

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	02/2025

Policy Type: PA/SP Pharmacy Coverage Policy: UMP251

Split Fill Management*

Description

Asciminib (Scemblix) is an orally administered BCR-ABL1 tyrosine kinase inhibitor (TKI) specifically targeting the ABL myristoyl pocket (STAMP) of BCR-ABL protein.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
asciminib (Scemblix)	20 mg tablets	Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CP-CML) with resistance or intolerance to two prior tyrosine kinase inhibitors	60 tablets/30 days*
	40 mg tablets		60 tablets/30 days*
asciminib (Scemblix)	20 mg tablets	Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CP-CML) with T315I mutation	60 tablets/30 days*
	40 mg tablets		300 tablets/30 days*
	100 mg tablets		120 tablets/30 days*

**Quantity exceptions are not allowed.*

Initial Evaluation

I. **Asciminib (Scemblix)** 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 will not be used in combination with any other BCR-ABL1 tyrosine kinase inhibitor (e.g., imatinib [Gleevec], dasatinib [Sprycel], bosutinib [Bosulif]); **AND**
   D. A diagnosis of **Chronic Myeloid Leukemia (CML)** when the following are met:
      i. The member has chronic phase Philadelphia chromosome-positive CML (Ph+ CP-CML); **AND**
         a. Documented resistance, or intolerance to, two prior BCR-ABL1 tyrosine kinase inhibitors (TKIs) (e.g., imatinib (Gleevec), dasatinib

(Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), ponatinib (Iclusig)); **AND**

b. Requested total daily dose of asciminib (Scemblix) does not exceed 80 mg per day (40 mg twice a day); **OR**

ii. The member has chronic phase Philadelphia chromosome-positive CML (Ph+ CP-CML) with T315I mutation; **AND**

a. Ponatinib (Iclusig) has been ineffective, or not tolerated; **OR**

i. Documentation that the member has pre-existing cardiovascular and/ or hepatic comorbidity that precludes the use of ponatinib (Iclusig); **AND**

b. Requested total daily dose of asciminib (Scemblix) does not exceed 400 mg per day (200 mg twice a day)

II. Asciminib (Scemblix) is considered investigational when used for all other conditions, including but not limited to:

A. Newly diagnosed CP-CML not previously treated with a TKI

B. CML in accelerated phase (AP-CML) or blast phase (BP-CML)

C. Any myeloproliferative neoplasm other than CP-CML (e.g., acute myeloid leukemia (AML), chronic lymphocytic l CLL)

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 any other BCR-ABL1 tyrosine kinase inhibitor [e.g., imatinib (Gleevec), dasatinib (Sprycel), bosutinib (Bosulif)]; **AND**

IV. Member has exhibited improvement or stability of disease symptoms [e.g., complete cytogenic response (CCyR), major molecular response (MMR)]

Supporting Evidence

I. Asciminib (Scemblix) is a BCR-ABL1 tyrosine kinase inhibitor (TKI). Unlike previous generation TKIs, which bind to the ATP binding pocket on BCR-ABL1 protein, asciminib (Scemblix) is purported to specifically target the ABL myristoyl pocket (STAMP), thus named a STAMP-inhibitor. Asciminib (Scemblix) is the first BCR-ABL1 STAMP inhibitor, FDA-approved as a third-line treatment option after resistance or intolerance to two or more prior TKIs for the treatment of Philadelphia chromosome positive chronic phase Chronic Myeloid Leukemia (Ph+ CP-CML). Additionally, it may be a treatment option for PH+ CP-CML with T315I mutation. The NCCN guideline for CML has included asciminib (Scemblix) as a Category 2A recommendation in these settings.

II. Given the complexities involved in diagnosis and management of CML, therapy decisions regarding initiation of asciminib (Scemblix) must be made by, or under the supervision of, a specialist practicing in this setting, (e.g., an oncologist, hematologist).

III. Asciminib (Scemblix) has ongoing clinical trials in the setting of treatment of CML in combination with another TKI (e.g., imatinib). However, such combination therapy has not been sufficiently supported by available clinical data and/or FDA approval.

IV. CML is classified into three groups that help predict its outlook. The phases are based mainly on the number of immature white blood cells (blasts) in the blood or bone marrow. Different groups of experts have suggested different cutoffs to define the phases, but a common system (proposed by the World Health Organization (WHO)) is widely accepted, described below:

- Chronic Phase (CP-CML): Less than 10% blasts in their blood or bone marrow samples. Generally mild symptoms (if any) and usually respond to standard treatments. Most patients are diagnosed in the chronic phase.
- Accelerated Phase (AP-CML): If any of the following are true: Blood samples have > 15% but < 30% blasts; plasma basophils ≥ 20%; ≥ 30% plasma (peripheral) blasts and promyelocytes combined; Very low platelet counts (100 x 1,000/mm^3 or less); or new chromosome changes in the leukemia cells with the Philadelphia chromosome.
- Blast phase (acute phase or blast crisis): Bone marrow and/or blood samples have ≥ 20% blasts. Large clusters of blasts are seen in the bone marrow. The blast cells have spread to tissues and organs beyond the bone marrow. CML acts like an AML in this phase.

V. Asciminib (Scemblix) is an oral tablet taken once or twice a day (dose based on indication) and is available as a 20 mg and 40 mg formulation. The dose for CP-CML refractory to ≥ 2 TKI is up to 80 mg per day (40 mg BID), while in the setting of CP-CML with T315I mutation, recommended dose of asciminib (Scemblix) is 200 mg twice a day. Dose reductions may be necessary due to drug related adverse reactions. Consequently, 20 mg tablet may be necessary to achieve dose modification for members requiring a lower dose. However, it should be noted that any increments of dosing up to 200 mg (each dose) may be achievable by use of a maximum 60 tablets of asciminib (Scemblix) 20 mg tabs. Similarly, in the setting of CP-CML refractory to ≥ 2 TKI, based on the maximum recommended dose (80 mg per day), quantity limit exceptions to asciminib (Scemblix) 40 mg tablet are not advised given excessive additional cost.

VI. More than 95% cases of CML are caused by the BCR-ABL1 fusion gene (Ph chromosome) and are usually diagnosed in its chronic phase when the treatment is very effective for most patients. Current standard of care for the treatment of CP-CML involves use of BCR-ABL1 TKI and allogenic hematopoietic cell transplant (HCT). First-generation TKI (imatinib) is the preferred initial therapy for patients with low-risk scores, while second-generation TKI (e.g., bosutinib, dasatinib, nilotinib) are the preferred regimens for intermediate or high-risk cases of CP-CML. The NCCN treatment guideline for CML recommends use of an alternative second-generation TKI for CP-CML refractory to first-generation TKI. Ponatinib (Iclusig) is a third-line therapy option for CP-CML resistant to at least two prior TKIs, or for patients with T315I mutation. Additionally, omacetaxine (Synribo) is recommended in cases with T315I mutation and on progression from CP-CML to accelerated phase CML (AP-CML).

VII. Clinical Trials: Asciminib (Scemblix) was evaluated in two open-label clinical trials, one for each FDA-approved indication, a Phase 3 randomized trial (ASCEMBL) and a Phase 1, single-arm trial (X2101).

- Phase 3: A randomized (2:1), open-label trial of asciminib (Scemblix) (40 mg BID) versus bosutinib (Bosulif) (500 mg QD) as active comparator. This trial was designed for the treatment of CP-CML in adult patients (N=233) refractory to ≥ 2 TKIs or

intolerance to the most recent TKI therapy. The rate of major molecular response (MMR) at week 24 was the primary endpoint along with MMR and rate of complete cytogenic response (CCyR) at 96 weeks, as key secondary endpoints. Known T315I mutations were excluded. At Week 24, the MMR rate was 25.5% for patients receiving asciminib (Scemblix) and 13.2% for those receiving bosutinib (Bosulif). The between-arm common treatment difference was 12.2% (95% CI: 2.19, 22.30; p=0.029). Additionally, asciminib arm reported a deep molecular response (MMR4.5; BCR-ABL1 < 0.0032%) in 10.8% (n=17) versus 5.3% (n=4) for those in bosutinib (Bosulif) arm.

- Phase 1: A single-arm dose exploration trial (N= 150), which was expanded for assessing asciminib (Scemblix) in Ph+ CP-CML patients (n=52) with T315I mutation. Majority of patients were refractory to ≥ 2 prior TKI therapies, however patients with T315I mutation were enrolled if refractory to one prior TKI. Although the primary endpoint was determination of maximum tolerated dose of asciminib (Scemblix), MMR was used as an objective measure of efficacy. At week 24, four out of 17 evaluable patients (24%) in the T315I+ CML cohort, who did not have MMR at baseline, achieved MMR (BCR-ABL ≤0.1%).

VIII. Asciminib (Scemblix) received accelerated FDA-approval as a third-line treatment for Ph+ CP-CML, refractory to two or more TKI therapies, and a full FDA-approval for treatment of CP-CML with T315I mutation. Continued approval in the third-line treatment setting remains contingent upon verification of clinical benefits in confirmatory trials.

IX. The safety data of asciminib (Scemblix) was based on all participants exposed to therapy. The most common adverse events (AE) included: Phase 1 trial: fatigue, increased lipase, thrombocytopenia, and hypertension. Phase 3 trial: 89.7% of patients in the asciminib arm and 96.1% of patients in the bosutinib arm experienced an AE with most common AE: diarrhea, increased ALT, and AST. Participants in the asciminib (Scemblix) arm reported significantly higher neutropenia (21.8% versus 21.1%) and thrombocytopenia (28.8% versus 18.4%) compared to bosutinib (Bosulif). During the Phase 3 clinical trial, asciminib (Scemblix) led to 36% dose reductions and 52% therapy interruptions, majority due to AE.

X. Asciminib (Scemblix) has not been compared with ponatinib (Iclusig) in head-to-head clinical trials. The majority of the safety and efficacy data for the use of TKIs in the setting of T315+ CP-CML are rooted in the previous clinical trials and established real-world efficacy and safety data of ponatinib (Iclusig). Additionally, omacetaxine (Synribo), a protein synthesis inhibitor, is indicated for the treatment of CP-CML with T315I mutation. Prescribing information for ponatinib (Iclusig) includes warnings and precautions related to cardiovascular toxicities, hepatic impairment, pancreatitis, hypertension, neuropathy, among others. It should be noted that proposed benefit of asciminib (Scemblix) over ponatinib (Iclusig) may be based on purported safety profile and lack of severe adverse events in the clinical trial population. The real-world long-term safety of asciminib (Scemblix) remains unknown. Weighing the safety, efficacy, cost, and clinical experience, ponatinib (Iclusig) may be considered an appropriate high-value treatment option in this space. Coverage of asciminib (Scemblix) in ponatinib-naïve population may be considered based on medical necessity (e.g., history of cardiovascular disorders, un-controlled hypertension etc.).

Investigational or Not Medically Necessary Uses

I. There are several clinical trials underway for assessing efficacy of asciminib (Scemblix) in the first-line treatment setting for CML as well as in combination with other TKIs. Trials have not been completed, and safety and efficacy in this setting and/or as a combination therapy remain unknown.
II. Asciminib (Scemblix) has not been FDA-approved, or sufficiently studied for safety and efficacy for the treatment of other conditions or settings, including CML in accelerated phase (AP-CML) or blast phase (BP-CML).

** 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. Rea D, Mauro MJ et al. A Phase 3, Open-Label, Randomized Study of Asciminib, a STAMP Inhibitor, vs Bosutinib in CML After ≥2 Prior TKIs. Blood. 2021 Aug 18: blood.2020009984. doi: 10.1182/blood.2020009984. PMID: 34407542.
2. Hughes TP, Mauro MJ, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med. 2019 Dec 12;381(24):2315-2326.
3. NCCN Clinical practice Guidelines in Oncology for chronic myeloid leukemia; V2.2022; updated November 15th, 2021.
4. Novartis. Scemblix (asciminib) [Prescribing Information]. 2021. Novartis Pharmaceutical Corp.; East Hanover, NJ.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 100mg tablets to the QL table	07/2024
Policy created	02/2022

Policy Type: PA Pharmacy Coverage Policy: UMP006

Description

Asfotase alfa (Strensiq™) is a tissue nonspecific alkaline phosphatase fusion protein considered a form of enzyme replacement therapy.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
asfotase alfa (Strensiq)	18mg/0.45mL vial	infantile, pediatric, or juvenile onset hypophosphatasia	24 vials/28 days
	28mg/ 0.7mL		24 vials/ 28 days
	40mg/ 1 mL vial		24 vials/ 28 days
	80mg/ 0.8 mL vial		24 vials/ 28 days

*See appendix A for dose recommendations

Initial Evaluation

I. Asfotase alfa (Strensiq) may be considered medically necessary when the following criteria below are met:
   A. Diagnosis is made by, or in consultation with, a geneticist, metabolic specialist, endocrinologist, or bone and mineral specialist; **AND**
   B. A diagnosis of **perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP)** when the following are met:
      1. Documented tissue-non-specified alkaline phosphatase (TNSALP) gene mutation status; **OR**
      2. Documented serum alkaline phosphatase (ALP) level below the age and gender-adjusted normal range; **AND**
         i. Elevated TNSALP substrate levels as determined by age and gender specific reference range of one of the following:
            a. Plasma pyridoxal-5'-phosphate (PLP); **OR**
            b. Urine concentration of phosphoethanolamine (PEA); **OR**
            c. Urinary inorganic pyrophosphate level (PPi); **AND**
      3. Onset of perinatal/infantile or juvenile-onset HPP occurring prior to the age of 18, as documented by signs and/or symptoms (e.g., respiratory insufficiency, vitamin B6 responsive seizures, failure to thrive, delayed walking, waddling gait, dental abnormalities, low trauma fracture, etc.); **OR**
         i. Radiographic evidence supporting the diagnosis of HPP prior to the age of 18 (e.g. craniosynostosis, infantile rickets, non-traumatic fracture); **AND**
         ii. Provider attestation member will be monitored for ectopic calcification

II. Asfotase alfa (Strensiq) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Adult-onset HPP
   B. Odontohypophosphatasia
   C. Pseudophypophosphatasia
   D. Other forms or causes of osteomalacia: X-linked hypophosphatemia, low bone mass, inappropriate treatment with bisphosphonates, osteoporosis

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. Diagnosis is made by, or in consultation with, a geneticist, metabolic specialist, endocrinologist, or bone and mineral specialist; **AND**
IV. A diagnosis of **perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP)**; **AND**
V. Documentation of a positive response to therapy with asfotase alfa, which includes improvement and/or stabilization in the clinical signs and symptoms of hypophosphatasia (e.g. improvement in ALP/PLP/PEA/PPi levels, improvement in respiratory function/breathing, weight gain, improvement in milestones, absence of new fractures/reduction in fracture occurrence, radiographic evidence of improvement, etc).

Supporting Evidence

I. Perinatal/infantile and juvenile-onset HPP are the pediatric variants of hypophosphatasia, which is a rare genetic disorder that impairs bone metabolism. HPP is associated with a high mortality rate, with survival rate estimated at less than 50% by one year of age in infancy due to rachitic deformities developed by six months of age; the diagnosis is lethal in the perinatal setting. Juvenile HPP is associated with premature loss of deciduous teeth, delayed walking, and waddling gait. Due to the risk of fractures, bone deformities and failure to thrive, there is risk for abnormal growth and development in pediatric patients diagnosed with perinatal/infantile or juvenile-onset HPP.
   - Approval by the FDA was based on three pivotal trials (ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10) conducted in 13 pediatric patients (five subjects with perinatal/infantile-onset HPP; eight subjects with juvenile-onset HPP).
      i. A Kaplan-Meier analysis of pooled overall survival data (n=68) was compared with a natural history group (n=48). This analysis showed an overall survival rate of 91% (n=68) of treated subjects when compared with 27% (n=48) of the historical control group.
      ii. In the juvenile-onset population, efficacy was assessed based on the Tinetti Modified Performance Oriented Mobility Assessment – Gait (mPOMA-G) scale. It was agreed by the FDA that change in gait is considered a surrogate marker and is not interpreted as an improvement in clinical outcomes. Radiographic analysis showed improvement in all subjects with treatment; however, using change in rickets severity and assessed by the Radiographic Global Impression of Change (RGI-C) scale, when compared to control group.

- HPP is a broadly expressed disorder ranging from death to arthropathy without bone disease. Prognosis is largely based on skeletal complications, with the most severe disease affecting patients with perinatal/infantile or juvenile-onset of HPP.
- Adult-onset hypophosphatasia is characterized by poor healing, bone pain, recurrent fracture, and increased incidence of pyrophosphate arthropathy and chondrocalcinosis. As onset presents during middle-age, the benefit of enzyme replacement in the adult population is unknown.
- The presence of a defective TNSALP allele without sign or symptoms of dental or arthritic complications helps determine the patient is a carrier only.
- As ectopic calcification has been reported, monitoring for ectopic calcification by means of ophthalmic examination and renal ultrasound is recommended by label at baseline and periodically throughout treatment.

Investigational or Not Medically Necessary Uses

I. Adult-onset HPP
   A. Asfotase alfa (Strensiq) is FDA-indicated for the treatment of members with perinatal/infantile- and juvenile-onset HPP; these populations are known to have the most severe disease and the benefit of enzyme replacement therapy is supported by data.
   B. There are limited to no research studies to support the efficacy of asfotase alfa (Strensiq) in the setting of adult-onset HPP without history of infantile and/or juvenile onset HPP. Evidence is currently limited to case-reports only.
   C. Adult-onset HPP treatment is currently limited to supportive therapy.

II. Odontohypophosphatasia
   A. Odontohypophosphatasia, expressed in dental complications alone, is the mildest and most prevalent form of hypophosphatasia. This diagnosis is typically associated with otherwise normal and/or good health condition.

III. Pseudohypophosphatasia
   A. Resembles infantile hypophosphatasia, however, without low serum alkaline phosphatase. Use of age-dependent reference range is important to differentiate between infantile-onset and pseudohypophosphatasia, or simply a transient elevation in TNSALP substrate.
   B. Causes of pseudohypophosphatasia can include, but are not limited to: cardiac bypass surgery, Celiac disease, Cushing syndrome, hypothyroidism, multiple myeloma, starvation, certain vitamin or mineral deficiencies or intoxications, or improperly collected blood sampling.

IV. Other forms or causes of osteomalacia: X-linked hypophosphatemia, low bone mass, inappropriate treatment with bisphosphonates, osteoporosis.

Appendix

Weight-Based Dosing for Administration of **2 mg/kg** three times per week

Body Weight (kg)	Dose to Inject	Volume to Inject	Vial Configuration	Number of Vials per 28 days
3	6 mg	0.15 mL	18mg/0.45mL	12
4	8 mg	0.2 mL	18mg/0.45mL	12
5	10 mg	0.25 mL	18mg/0.45mL	12
6	12 mg	0.3 mL	18mg/0.45mL	12
7	14 mg	0.35 mL	18mg/0.45mL	12
8	16 mg	0.4 mL	18mg/0.45mL	12

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

9	18 mg	0.45 mL	18mg/0.45mL	12
10	20 mg	0.5 mL	28mg/0.7kmL	12
15	30 mg	0.75 mL	40mg/mL	12
20	40 mg	1 mL	40mg/mL	12
25	50 mg	1.25 mL	Two 28mg/0.7mL	24
30	60 mg	1.5 mL	Two 40mg/mL	24
35	70 mg	1.75 mL	Two 40mg/mL	24
40	80 mg	0.8 mL	80mg/0.8mL	12
50	100 mg	1 mL	Two 80mg/0.8mL	24
60	120 mg	1.2 mL	Two 80mg/0.8mL	24
70	140 mg	1.4 mL	Two 80mg/0.8mL	24
80	160 mg	1.6 mL	Two 80mg/0.8mL	24

Weight-Based Dosing for Administration of **1 mg/kg** six times per week

Body Weight (kg)	Dose to Inject	Volume to Inject	Vial Configuration	Number of Vials per 28 days
3	3 mg	0.08 mL	18mg/0.45mL	24
4	4 mg	0.1 mL	18mg/0.45mL	24
5	5 mg	0.13 mL	18mg/0.45mL	24
6	6 mg	0.15 mL	18mg/0.45mL	24
7	7 mg	0.18 mL	18mg/0.45mL	24
8	8 mg	0.2 mL	18mg/0.45mL	24
9	9 mg	0.23 mL	18mg/0.45mL	24
10	10 mg	0.25 mL	18mg/0.45mL	24
15	15 mg	0.38 mL	18mg/0.45mL	24
20	20 mg	5 mL	28mg/0.7mL	24
25	25 mg	1.63 mL	28mg/0.7mL	24
30	30 mg	0.75 mL	40mg/mL	24
35	35 mg	0.88 mL	40mg/mL	24
40	40 mg	1 mL	40mg/mL	24
50	50 mg	0.5 mL	80mg/0.8mL	24
60	60 mg	1.6 mL	80mg/0.8mL	24
70	70 mg	0.7 mL	80mg/0.8mL	24
80	80 mg	0.8 mL	80mg/0.8mL	24

References

1. Strensiq [package insert]. Cheshire, CT: Alexion Pharmaceuticals; January 2018.
2. Whyte MP. Hypophosphatasia- aetiology, nosology, pathogenesis, diagnosis and treatment. Nature Reviews Endocrinology, 2016. I12: 233-246. Available at https://www.nature.com/articles/nrendo.2016.14 [Accessed September 9, 2019].
3. Update on the Management of Hypophosphatasia. Therapeutic Advances in Musculoskeletal Disease. Sage Journals; 2019 June.
4. Cohen A, and Drake MT (2019) Epidemiology and etiology of osteomalacia. In J.A. Melin (Ed.) UpToDate. Retrieved September 9, 2019 from https://www-uptodate-com.liboff.ohsu.edu/contents/epidemiology-and-etiology -of-osteomalacia.
5. FDA [Online Press Release]. FDA approves new treatment for rare metabolic disorder. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm468836.htm [Accessed November 2, 2015]
6. National Organization for Rare Disorders. Hypophosphatasia. Available at: https://rarediseases.org/rare-diseases/hypophosphatasia/ [Accessed November 2, 2015]
7. Beck C., Morbach H., Stenzel M., Colmann H., Schneider P., and Girschick HJ. Hypophosphatasia- Recent Advances in Diagnosis and Treatment. The Open bone Journal, 2009; I:8-15. Available at: http://benthamopen.com/contents/pdf/TOBONEJ/TOBONEJ-1-8.pdf [Accessed November 2, 2015]

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated the age of onset of symptoms from 12 years of age to 18 years of age. Updated renewal criteria to be limited to requirements around being prescribed by a specialist, confirmation of indication, and documented improvements in signs/symptoms rather than repetition of all initial criteria.	12/2020
Transfer to policy format. Added NMC and Supportive Evidence sections. Addition of criterion for appropriate diagnosis, as is recommended by compendia and medical literature. Addition of requirement of diagnosis by a specialist: diagnosis requires assessment of multiple laboratory levels, and combined/compared with clinical presentation. Potential for differential diagnosis is high. Change to initial approval of six months and renewal at 12 months from 3 month initial approval and 6 month renewal. As the overall benefit of Strensiq is seen over the course of pediatric development, a longer renewal period was implemented.	09/2019
Previous reviews	8/2017
Policy created	11/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP237

Description

Avacopan (Tavneos) is a complement C5a receptor antagonist for the treatment of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
avacopan (Tavneos)	10 mg capsules	Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis	180 capsules/30 days

Initial Evaluation

I. **Avacopan (Tavneos)** 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 nephrologist, rheumatologist, pulmonologist, or a specialist in the treatment of vasculitis associated disorders; **AND**
   C. A diagnosis of **antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV)** when the following are met:
      1. Diagnosis is classified as **granulomatosis with polyangiitis (GPA)** or **microscopic polyangiitis (MPA)**; **AND**
      2. Presence of organ-threatening manifestations (e.g., severe and progressive kidney involvement, severe lung or nervous system involvement); **AND**
      3. Treatment with high dose glucocorticoids in combination with standard of care agents (e.g., cyclophosphamide, rituximab) has been ineffective, contraindicated, or not tolerated; **AND**
      4. INDUCTION: Medication will be used in combination with cyclophosphamide or rituximab (e.g., Rituxan, Ruxience); **AND**
      5. MAINTENANCE: Medication will **NOT** be used in combination with rituximab (e.g., Rituxan, Ruxience)

II. Avacopan (Tavneos) is considered investigational when used for all other conditions, including but not limited to:
   A. MPA or GPA in patients less than 12 years of age
   B. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
   C. Systemic lupus erythematosus

D. IgA vasculitis
E. Rheumatoid vasculitis

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 maintenance treatment, medication will **NOT** be used in combination with rituximab (e.g., Rituxan, Ruxience); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., achievement of long-standing remission, decrease in rates of relapse); **OR**
V. Medication will be used for induction treatment in combination with cyclophosphamide or rituximab (e.g., Rituxan, Ruxience)

Supporting Evidence

I. ANCA-associated vasculitis (AAV) are a group of rare autoimmune disorders characterized by inflammation and destruction of small to medium-sized blood vessels and presence of circulating ANCA. Specific subtypes include GPA, MPA, renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis (EGPA). The presentation of AAV is highly variable and spectrum of disease may range from relatively mild and localized to the upper respiratory tract to life-threatening involvement of multiple organ systems. If left untreated AAV is a fatal disorder, with the main cause of death due to respiratory or renal failure.
II. Assessment of AAV requires expert guidance to differentiate activity from damage or infection and to consider differential diagnoses. Patients may require interventions by multiple different specialists depending on organ involvement and disease severity and may require services such as immunological monitoring, specialized radiography, assessment of eye involvement, and renal transplantation. The 2015 European League Against Rheumatism (EULAR) clinical guidelines recommend that all AAV patients should be managed in close collaboration with, or at, centers of expertise (Grade of recommendation: C).
III. The diagnosis of GPA or MPA is suspected in patients presenting with constitutional symptoms (e.g., fever, weight loss, arthralgias) with clinical evidence of renal or respiratory tract involvement. Testing for ANCA should be performed using assays for proteins within neutrophils called proteinase 3 (PR3) and myeloperoxidase (MPO). Approximately 82 to 94 percent of patients with either GPA or MPA have a positive ANCA, depending on severity of disease. GPA is primarily associated with PR3-ANCA (65 to 75 percent of cases), while MPA is primarily associated with MPO-ANCA (55 to 65 percent of cases). A negative assay does not exclude the diagnosis of GPA or MPA and ANCA status may change over time. Tissue biopsies should be considered in cases of suspected AAV to confirm diagnosis. Tissue biopsy is particularly important in patients who are ANCA-negative or in whom there is a degree of diagnostic uncertainty. A negative or “nondiagnostic” biopsy does not exclude a diagnosis of AAV as diagnostic sensitivities vary depending on the organ biopsied.

IV. Disease severity is characterized as either organ or life threatening or non-organ threatening. Examples of non-organ threatening disease include skin involvement without ulceration, myositis, nasal, and paranasal disease without bony involvement or cartilage collapse. For non-organ threatening disease treatment with methotrexate or mycophenolate is preferred. For organ or life threatening disease, treatment with cyclophosphamide or rituximab is indicated.

V. Treatment of patients with AAV is comprised of two phases: induction and maintenance. Induction treatment typically lasts for three-to-six months with the goal of establishing remission. For some induction may extend for longer than 6 months, however this is not common. The optimal duration of maintenance is unknown. Therapy for induction and maintenance is chosen based on the severity of disease. The 2015 EULAR clinical guidelines recommend induction treatment based on severity of the disease:

Induction/relapse

- New onset organ-threatening or life threatening AAV – combination of high-dose glucocorticoids and either cyclophosphamide OR rituximab (Grade of recommendation: A)
- Non-organ threatening AAV – combination of high-dose glucocorticoids and either methotrexate or mycophenolate mofetil (Grade of recommendation: B for methotrexate, C for mycophenolate mofetil)

Maintenance: Combination of low-dose glucocorticoids initially and either azathioprine, rituximab, methotrexate or mycophenolate mofetil for at least 24 months following sustained remission (Grade of recommendation: A)

VI. Avacopan (Tavneos) was studied in one 52-week, randomized, double-blind, double-dummy, Phase 3 clinical trial in 331 patients with newly diagnosed or relapsed GPA or MPA, in whom treatment with cyclophosphamide or rituximab was indicated. Enrolled patients were 12 years of age or older, with median patient age of 61 years. Avacopan (Tavneos) was studied at an oral dose of 30 mg twice daily against oral prednisone taper over a 21-week period (6 0mg, 45 mg for patients <55 kg and 30 mg for patients <37 kg per day starting dose). All patients received cyclophosphamide followed by azathioprine (or mycophenolate mofetil) or rituximab. Patients were allowed to receive glucocorticoid rescue therapy and to continue glucocorticoids for non-vasculitis reasons. The primary efficacy outcomes were clinical remission at week 26 and sustained remission at week 52 and no receipt of glucocorticoids for 4 weeks before evaluation of efficacy endpoints.

Primary Endpoints	Avacopan (n=166)	Prednisone (n=164)	Difference (95% CI)	p-value
Remission at wk 26, no %	120 (72.3)	115 (70.1)	3.4 (-6.0-12.8)	**Noninferiority: p<0.001** Superiority: p=0.24
Sustained remission at wk 52, no %	109 (65.7)	90 (54.9)	12.5 (2.6-22.3)	**Noninferiority: p<0.001 Superiority: p=0.007**

VII. Safety profile of avacopan (Tavneos) is still developing and is limited to a small population, 166 patients who received at least one dose of avacopan (Tavneos) and 134 who received it for more than six months. Overall a similar proportion of patients in both treatment arms experienced adverse events (AEs), including serious adverse events (SAEs) and AEs leading to discontinuation. SAEs occurred in 42.2% vs 45.1% of the avacopan (Tavneos) and prednisone arms, respectively. Common SAEs included ANCA-positive vasculitis, 7.2% vs 12.2%; pneumonia, 4.8% vs 3.7%; GPA, 3% vs 0.6%; acute kidney injury 1.2% vs 0.6%; and urinary tract infection

1.8% vs 1.2% in the avacopan (Tavneos) and prednisone arms, respectively. There were more patients in the avacopan (Tavneos) group than in the prednisone group that experienced SAEs of abnormality on liver-function testing, 5.4% vs 3.7%, respectively. More patients experienced AEs related to glucocorticoids in the prednisone group than in the avacopan (Tavneos) group, 80.5% vs 66.3%, respectively.

VIII. The place in therapy for avacopan's (Tavneos) is evolving; however, it is currently limited by evidence gathered from one Phase 3 clinical trial with a small safety database. High dose glucocorticoids have a known safety profile and remain highly effective when used in combination with the standard of care (e.g., cyclophosphamide, rituximab) to induce remission. This coupled with absence of significant differences in the observed adverse events seen in patients treated with avacopan (Tavneos), makes high dose glucocorticoids an appropriate first-line treatment option. Though there were fewer steroid related adverse events noted in the avacopan (Tavneos) arm during the pivotal clinical trial, the majority of adverse events expected with a prednisone taper when starting with a high dose are predictable, manageable, and transient. At this time, insight to the safety profile and cost-effectiveness of glucocorticoids are favorable to avacopan (Tavneos).

IX. Maintenance therapy is initiated after successful induction of remission. Avacopan (Tavneos) has not been studied in combination with rituximab as maintenance therapy. Further studies are needed to establish safety and efficacy of this combination therapy. At this time it is unknown whether efficacy may be additive if these therapies are used in combination, and safety of this combination is unknown.

Investigational or Not Medically Necessary Uses

I. Avacopan (Tavneos) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. MPA or GPA in patients less than 12 years of age
   B. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
   C. Systemic lupus erythematosus
   D. IgA vasculitis
   E. Rheumatoid vasculitis

References

1. Jayne DRW, Merkel PA, Schall TJ, Bekker P; ADVOCATE Study Group. Avacopan for the Treatment of ANCA-Associated Vasculitis. N Engl J Med. 2021;384(7):599-609. doi:10.1056/NEJMoa2023386
2. Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitisAnnals of the Rheumatic Diseases 2016;75:1583-1594.
3. McGeoch L, Twilt M, Famorca L, et al. CanVasc Recommendations for the Management of Antineutrophil Cytoplasm Antibody-associated Vasculitides. J Rheumatol. 2016;43(1):97-120. doi:10.3899/jrheum.150376
4. U.S. Food and Drug Administration. Office of Immunology and Inflammation. (2021). *FDA Briefing Document.* Available at: https://www.fda.gov/media/148176/download.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria in the renewal section which ensures medication will not be used in combination with rituximab for maintenance and if used for induction treatment, medication will be used in combination with cyclophosphamide or rituximab and does not require attestation of achieved remission.	01/2022

Policy created	08/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP007

Split Fill Management*

Description
Axitinib (Inlyta) is an orally administered tyrosine kinase inhibitor, including vascular endothelial growth factor receptors (VEGFR) that are responsible for tumor growth, angiogenesis, and disease progression.

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

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
axitinib (Inlyta)	1 mg tablets	Advance renal cell carcinoma	240 tablets/30 days
	5 mg tablets		120 tablets/30 days

Initial Evaluation

I. Axitinib (Inlyta) may be considered medically necessary when the following criteria below are met:
   A. Axitinib (Inlyta) is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   B. A diagnosis of **Advanced Renal Cell Carcinoma (Relapsed or Stage IV)** when the following are met**:**
      1. Axitinib (Inlyta) will be used as monotherapy; **AND**
      2. Prior treatment with one of the following has been ineffective or not tolerated, unless ALL are contraindicated.
         i. sunitinib (Sutent)
         ii. temsirolimus (Torisel)
         iii. bevacizumab (Avastin)
         iv. pazopanib (Votrient)
         v. sorafenib (Nexavar)
         vi. everolimus (Afinitor); **OR**
      3. Axitinib (Inlyta) will be used in combination with pembrolizumab (Keytruda) as first-line therapy; **OR**
      4. Axitinib (Inlyta) will be used in combination with avelumab (Bavencio) as first-line therapy

II. Axitinib (Inlyta) is considered investigational when used for all other conditions, including but not limited to:

A. Non-metastatic Stage I-III Renal Cell Carcinoma

Renewal Evaluation

I. Tumor response is documented with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
II. The member has an absence of unacceptable toxicity from the medication

Supporting Evidence

I. Axitinib (Inlyta) is indicated for advance renal cell carcinoma (RCC) after failure of one prior systemic therapy; or as first-line therapy when used in combination with pembrolizumab (Keytuda); or as first-line therapy when used in combination with avelumab (Bavencio).
II. The FDA approval of axitinib (Inlyta) in the setting of advanced RCC after failure of one prior systemic therapy was based on the results of a phase 3 trial (AXIS). In the AXIS trial, the primary end point was progression free survival in the intention-to-treat population. The median PFS was 6·7 months with axitinib compared to 4·7 months with sorafenib (hazard ratio 0·665; 95% CI 0·544-0·812; one-sided p<0·0001).
    - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).
III. The FDA approval of pembrolizumab (Keytruda) in combination with axitinib (Inlyta) was based on the results of KEYNOTE-426, an open-label, phase 3 trial. In the KEYNOTE-426 trial, the primary end points were overall survival and progression-free survival in the intention-to-treat population. Statistical significance as achieved after a median follow-up of 12.8 months, the estimated percentage of untreated advanced RCC patients who were alive at 12 months was 89.9% in the pembrolizumab-axitinib group compared to 78.3% in the sunitinib group.
    - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).
IV. The FDA approval of avelumab (Bavencio) in combination with axitinib (Inlyta) was based on positive results from the Phase III JAVELIN Renal 101 study, involving previously untreated advanced RCC patients. In the JAVELIN Renal 101 study, the median progression-free survival was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib.
    - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).

Investigational or Not Medically Necessary Uses

I. Non-metastatic Stage I-III Renal Cell Carcinoma
    A. Axitinib (Inlyta) has not been studied in non-metastatic, non-advanced (stage I-III) renal cell 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. Inlyta [Prescribing Information]. New York, NY: Pfizer, Inc. August 2018.
2. Keytruda [Prescribing Information]. White House Station, NJ: MERCK & CO, Inc. April 2019.
3. Bavencio [Prescribing Information]. Rockland, MA: EMD Serono, Inc. May 2019.
4. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011 Dec 3;378(9807):1931-9. Doi: 10.1016/S0140-6736(11)61613-9.
5. Motzer R, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 380:1103-1115. Doi:10.1056/NEMJMoa1816047.
6. Rini B.I, Plimack E.R, Stus V., et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Feb 380:1116-1127. Doi:10.1056/NEMJMoa1816714.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transitioned criteria to policy. In this transition, the following updates were made: added new indication for advance renal cell carcinoma to use axitinib (Inlyta) in combination with pembrolizumab (Keytruda) or avelumab (Bavencion) as first-line therapy.	06/2019
Previous Updates	03/2016; 04/2016; 06/2019;
Policy Update	07/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP2018

Description

Azacitidine (Onureg) is an orally administered hypomethylating agent (HMA).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
azacitidine (Onureg)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission	200 mg tablet	14 tablets/28 days
		300 mg tablet	

Initial Evaluation

I. **Azacitidine (Onureg)** 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 will be used as monotherapy; **AND**
   D. A diagnosis of **acute myeloid leukemia (AML)** when the following are met:
      1. Provider attestation the member has intermediate or poor-risk disease; **AND**
      2. Member has achieved first complete remission (CR) after induction chemotherapy (e.g. cytarabine, idarubicin, daunorubicin, mitoxantrone); **AND**
      3. Member received at least one cycle of consolidation chemotherapy; **OR**
         i. Provider attests that the member is not able to receive any or all of the recommended consolidation therapy; **AND**
      4. Provider attests that the member is ineligible for allogenic hematopoietic stem cell transplant (HSCT); **AND**
   E. Treatment with IV or subcutaneous (SC) azacitidine (Vidaza) or IV decitabine (Dacogen) has been ineffective, contraindicated, or not tolerated

II. Azacitidine (Onureg) is considered Not Medically Necessary when used for:
   A. Treatment of Myelodysplastic syndrome (MDS)

III. Azacitidine (Onureg) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute myeloid leukemia- newly diagnosed (Induction chemotherapy)

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

B. Acute myeloid leukemia – maintenance following allogenic HSCT
C. Acute myeloid leukemia – relapsed after first remission
D. In combination with other oncolytic agents

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. Disease response to treatment defined by stabilization or improvement of disease (e.g. maintenance of remission; lack of disease relapse or progression)

Supporting Evidence

I. Azacitidine (Onureg) is an orally administered HMA FDA-approved for the treatment of AML in patients aged 18 years and older. It is indicated for patients who have achieved first CR after induction chemotherapy and/or consolidation therapy.
II. Many treatment options exist for AML. Initial and further line therapies in this setting are contingent upon patient specific characteristics, disease-risk, and cytogenetic stratification. Given the complexities surrounding diagnosis and treatment choices, azacitidine (Onureg) must be prescribed by or in consultation with an oncologist or hematologist.
III. Currently, AML treatment is stratified by patient age, cytogenetic and molecular risk status, actionable mutations, AML disease characteristics and classification, and the patient's ability to tolerate intensive therapy based on comorbidities and performance status. Patients with AML are encouraged to enroll in clinical trials during any phase of treatment. Initial induction therapy for AML usually involves use of antimetabolite (e.g. cytarabine) in combination with anthracycline analogs (e.g. daunorubicin), also known as 7+3 regimen. Although majority of patients achieve CR, or complete remission with incomplete blood count recovery (CRi), post induction therapy, consolidation chemotherapy is recommended in order to prolong remission.
IV. Historically, induction therapy utilizing an intensive chemotherapy regimen (e.g., cytarabine and an anthracycline) has been the standard of care in AML patients with a good performance status who can tolerate aggressive initial treatment. Post-remission therapy, which includes consolidation, allogeneic HSCT, maintenance, and/or continued treatment, is tailored based on the patient's overall risk of AML relapse. Relapse rates for AML can be as high as 80% depending on patient age, cytogenetic and molecular abnormalities, and other factors. Intensive curative therapy (e.g., allogeneic HSCT) may not be a feasible option for many older patients due to comorbidities, poor performance status, and a high risk of transplant-related mortality. Additionally, some patients experience a deterioration in their condition between the start of induction and achievement of CR, others refuse HSCT, and disadvantaged populations with high levels of poverty and living in rural geographic counties have inferior access to HSCT, such that only a minority (8%) of treated patients with AML receive an allogeneic HSCT. In such cases, additional interventions to decrease the likelihood of relapse and improve survival are practical. Consolidation with successive cycles of AML-directed therapy may be recommended for patients

with relatively low risk of AML relapse, while allogeneic HSCT may be offered to eligible patients with intermediate and high risk of relapse. Azacitidine (Onureg) is indicated for continued treatment for adult patients, who had CR or CRi post induction chemotherapy, with or without consolidation, and who are unable to complete intensive curative therapy. NCCN guidelines for AML has included azacitidine (Onureg) as a maintenance therapy agent. However, consolidation chemotherapy is still a preferred option for patients with favorable risk cytogenetics and those who do not have comorbidities precluding use of intensive consolidation chemotherapy.

V. The use of azacitidine (Onureg) has not been studied in combination with other treatment regimens for AML, such as venetoclax (Venclexta) and midostaurin (Rydapt). Due to lack of safety and efficacy data with a combination regimen, these agents should not be used together. Additionally, there is no data to support efficacy of azacitidine (Onureg) in place of HSCT, which remains the curative therapeutic alternative for majority of patients.

VI. The efficacy and safety of azacitidine (Onureg) was evaluated in a Phase 3, double-blind, randomized, placebo-controlled trial (N= 472). Patient were randomized to receive an oral 300 mg dose of treatment or matching placebo for 14 days. Overall survival (OS) was the primary endpoint and relapse-free survival (RFS) was a key secondary outcome. Median treatment duration was 12 cycles. Patients included had intermediate or poor cytogenetic risk AML, who were not candidates for HSCT and had CR or CRi post induction and/or consolidation therapy. Patients with prior history of HMA were excluded. Overall survival for azacitidine (Onureg) treatment arm was 24.7 months (95% CI; 18.7, 30.5) as compared to that of 14.8 months (95% CI; 11.7, 17.6) for placebo the arm [hazard ratio 0.69 (95% CI; 0.55, 0.86; *p*= 0.0009]. Additionally, median RFS was 10.2 months vs 4.8 months for treatment vs placebo [HR 0.65 (95% CI; 0.52, 0.81; *p*= 0.0001)].

VII. During the clinical trial, dose escalation to a 21-day regimen of azacitidine (Onureg) was allowed for patients showing 5% to 15% bone marrow (BM) blasts during treatment phase. However, increased drug exposure did not lead to additional survival benefits. Currently, there is insufficient data to support a 21 day treatment cycle with azacitidine (Onureg).

VIII. The most common adverse events (AE) reported for azacitidine (Onureg) during clinical trial were nausea, vomiting, and diarrhea. Additionally, grade 3 to 4 hematological AEs such as neutropenia, thrombocytopenia, and febrile neutropenia were reported. Azacitidine (Onureg) treatment led to 13% treatment discontinuation, 43% dose interruption due to AEs, and 16% dose reduction rates.

IX. The NCCN guideline for the treatment of AML was updated in June 2022, which upgraded the recommendation to use oral azacitidine (Onureg) as a maintenance treatment for AML to a Category 1 recommendation. This recommendation is limited to patients, who are ≥ 55 years of age, have intermediate to poor cytogenetic risk, and have undergone a consolidation therapy, or are unable to receive any consolidation regimens. This criteria is consistent with the clinical trial design for azacitidine (Onureg) wherein majority of trial participants were ≥ 55 years of age. It is important to note that the efficacy and safety of azacitidine (Onureg) have not been compared with IV or subcutaneous azacitidine (Vidaza) via a head-to-head clinical trial and the current clinical data does not establish the superiority of oral azacitidine (Onureg) over IV or SC azacitidine (Vidaza). Additionally, IV and SC azacitidine formulations remain a guideline recommended alternative for patients ≥ 55 years (Category 2A recommendation). IV azacitidine is not contraindicated in patients ≥ 55 years, nor a dose adjustment is recommended based on age. Although not FDA approved, IV and SC formulations of azacitidine (Vidaza) have been

utilized as maintenance therapy of AML and are expected to remain mainstay treatment alternatives. For members < 55 years of age, who are medically fit, and are not candidates for HSCT, surveillance may be considered over maintenance therapy. Although NCCN guideline recommend use of oral azacitidine (Onureg) as a maintenance treatment in this population, the NCCN panel notes that the data surrounding the efficacy of azacitidine (Onureg) in this setting is limited to the older population (≥ 55 years of age). Additionally, as of June 2022, use of decitabine (Dacogen) as a maintenance therapy, has been updated to a Category 2B recommendation.

X. The majority of the safety and efficacy data for use of hypomethylating agents in the maintenance treatment of AML are rooted in the trials for the IV and SC therapies. Approval of azacitidine (Onureg) was based on the reported survival outcomes data of this oral formulation. However, there is no evidence to suggest superiority of oral azacitidine (Onureg) over IV/SC azacitidine (Vidaza) and/or IV decitabine (Dacogen). Weighing the safety, efficacy, cost, and clinical experience, IV/ SC therapies are considered standard and appropriate high-value treatment options in this space and are preferred over azacitidine (Onureg).

Investigational or Not Medically Necessary Uses

I. Efficacy and safety of azacitidine (Onureg) for treatment of MDS was studied in a Phase 3 trial wherein 300 mg of azacitidine (Onureg) or a matching placebo were administered once daily for 21 days per 28-day cycle in patients with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS (AZA-MDS-003). Although azacitidine (Onureg) treatment showed higher percentage of patients reporting RBC transfusion independence versus placebo, the study was halted due to safety concerns related to an excess of early mortality due to hematological toxicities in the treatment arm.

II. Azacitidine (Onureg) is currently being studied in multiple clinical trials in the settings of MDS maintenance post HSCT, for maintenance therapy after HSCT in patients with AML, and for induction chemotherapy for newly diagnosed AML. However, there are no published results for these trials indicating efficacy and safety of azacitidine (Onureg) in these conditions.

References

1. Azacitidine (Onureg) prescribing information. Summit, NJ: Celgene Corporation; September 2020.
2. Estey, E H. Acute myeloid leukemia: 2019 update on risk-stratification and management. *Am J Hematol*. 2018;93(10):1267-1291.
3. Narayanan D, Weinberg OK. How I investigate acute myeloid leukemia. *Int J Lab Hematol.* 2020; 42:3-15.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020; 70:7-30.
5. Garcia-Manero G, Savona MR, Gore SD, et al. CC-486 (oral azacitidine) in patients with hematological malignancies who had received prior treatment with injectable hypomethylating agents (HMAs): Results from phase 1/2 CC-486 studies. *Blood* (ASH Annual Meeting Abstracts) 2016b;128: Abstract 905.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
NCCN updated recommendation (Category 1) reviewed; PA policy unchanged; updated formatting and supporting evidence	11/2022
Policy created	02/2021

belimumab (Benlysta®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP112

Description

Belimumab (Benlysta) is a subcutaneously administered human IgG1 lambda monoclonal antibody that inhibits the binding of soluble human B lymphocyte stimulator protein (BLyS) to its receptors on the B cells.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
belimumab (Benlysta)	Systemic Lupus Erythematosus (SLE); Lupus Nephritis (LN)	200 mg/mL syringe	*4 syringes/28 days
		200 mg/mL autoinjector	*4 autoinjectors/28 days

**Does not include loading dose required for LN*

Initial Evaluation

I. **Belimumab (Benlysta)** may be considered medically necessary when the following criteria below are met:
   A. Member is five 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 other biologic(s)[e.g., rituximab (Rituxan), abatacept (Orencia), voclosporin (Lupkynis)]; **AND**
   D. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; **AND**
   E. A diagnosis of one of the following:
      1. **Systemic Lupus Erythematosus (SLE)**; **AND**
         i. A SLE Disease Activity Index (SELENA-SLEDAI) score of ≥ 8 supported by documentation in chart notes; **AND**
         ii. Documentation of baseline Physician's Global Assessment (PGA) score; **AND**
         iii. Treatment with **one** standard therapy agent from each category below, has been ineffective, contraindicated, or **ALL** are not tolerated:
            a. Antimalarials (e.g., chloroquine, hydroxychloroquine)
            b. NSAIDs (e.g., ibuprofen, naproxen)
            c. Immunosuppressive (e.g., azathioprine, mycophenolate mofetil, methotrexate); **OR**
      2. **Lupus Nephritis (LN); AND**
         i. Biopsy indicating class III (focal), IV (diffuse) or V (membranous) LN; **AND**
         ii. Biopsy shows active lesions or active AND chronic lesions; **AND**

iii. Provider attestation indicating medication will be given in combination with mycophenolate for induction and maintenance OR cyclophosphamide for induction followed by azathioprine for maintenance; **AND**

F. Provider attestation indicating member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated

II. Belimumab (Benlysta) is considered investigational when used for all other conditions, including but not limited to:
   A. Severe active central nervous system lupus

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 **Systemic Lupus Erythematosus (SLE**); **AND**
   A. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in SELENA-SLEDAI score or PGA score); **OR**
IV. A diagnosis of **Lupus Nephritis (LN)**; **AND**
   A. 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); **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. The safety and efficacy of belimumab (Benlysta) in the pediatric SLE population was studied via the intravenous formulation in an international, randomized, double blind, placebo-controlled, 52-week, trial involving 93 pediatric patients as young as five years of age. The primary efficacy endpoint was the SLE Responder Index (SRI-4) at Week 52; of the 53 randomized participants to the belimumab (Benlysta) arm, the SRI-4 was 53% while the placebo arm was 44% with an odds ratio of 1.49 and 95% CI (0.64, 3.46).
II. FDA approval of belimumab (Benlysta) in pediatric patients with lupus nephritis was based on the extrapolation of efficacy from the intravenous (IV) study in adults with active lupus nephritis, and supported by pharmacokinetic data from IV studies in adults with active lupus nephritis and from pediatric patients with SLE. The estimated Benlysta exposures for pediatric patients were comparable to adults with active lupus nephritis.
III. Belimumab (Benlysta) was shown to be ineffective in seronegative patients, and is therefore only indicated in patients with active SLE who are autoantibody positive (seropositive). Clinical trials in the setting of LN also included patients who are autoantibody positive.

IV. Per label, the use of belimumab (Benlysta) in combination with other biologics has not been studied and is not recommended.

Systemic Lupus Erythematosus (SLE)

V. The safety and efficacy of belimumab (Benlysta) administered subcutaneously were evaluated in a randomized, double-blind, placebo-controlled trial involving 836 patients with SLE. Patients with severe active lupus nephritis and severe active CNS lupus were excluded. The primary efficacy endpoint was the SRI-4 at Week 52; in the belimumab (Benlysta) arm SRI-4 was 61% compared to placebo 48% with an odds ratio of 1.7 and 95% CI (1.3, 2.3).

A. As reported in the trial baseline concomitant medications included corticosteroids (86%), antimalarials (69%), and immunosuppressives (46%, including azathioprine, methotrexate, and mycophenolate). Most patients (approximately 80%) were receiving 2 or more classes of SLE medications.

Lupus Nephritis (LN)

VI. LN is a kidney disease that develops in about 40% of patients with SLE with approximately 10% of patients with LN developing end stage renal disease (ESRD). Kidney failure, dialysis, and kidney transplants are all 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.

VII. 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.

VIII. The safety and efficacy of belimumab (Benlysta) in the setting of LN was evaluated in a randomized, double-blind, placebo-controlled trial involving 448 patients with Class III-V LN. Patients with severe active CNS lupus were excluded. The primary efficacy endpoint was renal

response (complete or no response) at week 104. Renal response was defined as urinary protein to creatinine ratio of <0.7, eGFR no worse than 20% below the pre-flare value or ≥60 ml per minute per 1.73 m2, and no rescue therapy. In the belimumab (Benlysta) arm renal response was 43% compared to placebo 32.3% with an odds ratio of 1.6 and 95% CI (1.0, 2.3), P= 0.0311.

- All patients included in the trial were on background therapy with mycophenolate mofetil or cyclophosphamide–azathioprine. Patients were 18 years of age and older with antibody positive SLE, ratio of urinary protein to creatinine > 1 or more, 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.

Investigational or Not Medically Necessary Uses

I. Severe active central nervous system lupus
   A. Per label, the use of belimumab (Benlysta) in the setting of severe active central nervous system lupus has not been evaluated, and efficacy has not been established; therefore, use is not recommended by the manufacturer in this setting.

References

1. Benlysta [Prescribing Information]. Philadelphia, PA: GlaxoSmithKline. July 2022.
2. 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.
3. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR Recommendation for The Management of Systemic Lupus Erethmatosus. Annals of the Rheumatic Diseases 2019;78:736-745. Available at: https://ard.bmj.com/content/78/6/736
4. Lam NC, Ghetu MV, and Bieniek M. Systemic Lupus Erythematosus: Primary Care Approach to Diagnosis and Management. Am Fam Physician. 2016 Aug 15;94(4):284-294. Available at: https://www.aafp.org/afp/2016/0815/p284.html
5. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383(12):1117-1128.
6. Belimumab and Voclosporin for Lupus Nephritis: Effectiveness and Value. Draft Evidence Report. Institute for Clinical and Economic Review (ICER). January 2021. Available at: https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Draft-Evidence-Report_012221.pdf
7. 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.

Policy Implementation/Update:

Action and Summary of Changes	Date
Expanded age requirement to five years and older.	10/2022
Added voclosporin (Lupkynis) in examples of biologics that cannot be used in combination with Benlysta	08/2021
Addition of new indication of lupus nephritis and further specified specialist to include nephrologist. Removal of criteria excluding concomitant use of cyclophosphamide	02/2021
Criteria transitioned into policy with the following updates made: addition of supporting evidence and investigational section, removal of active infection question, removal of vaccine question, updated renewal question relating to symptom improvement into one question, and removing specific symptom improvement parameters to be consistent with the market.	11/2019
Previous review	11/2017
Criteria created	09/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP239

Description

Belumosudil (Rezurock) is an orally administered Rho-associated kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
belumosudil (Rezurock)	200 mg tablets	Chronic graft-versus-host disease after failure of at least two prior lines of therapy	30 tablets/30 days*

*Quantity exceptions are not allowed.

Initial Evaluation

I. Belumosudil (Rezurock) 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 **chronic graft-versus-host disease (cGVHD)** when the following are met:
      1. Documentation of moderate-to-severe disease (e.g., Grade 2-4, or Grade B-D); **AND**
      2. Member is 12 years of age or older; **AND**
      3. The medication will not be used in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi); **AND**
      4. Member has had in inadequate response to two prior lines of systemic therapy for the treatment of cGVHD (e.g., corticosteroids, calcineurin inhibitors [tacrolimus, cyclosporin], mycophenolate, mTOR inhibitors [sirolimus], ibrutininb [Imbruvica], ruxolitinib [Jakafi]); **AND**
      5. Proton pump inhibitor therapy (e.g., omeprazole, pantoprazole, lansoprazole, esomeprazole) will not be used in combination with belumosudil (Rezurock).

II. Belumosudil (Rezurock) is considered <u>not medically necessary</u> when criteria above are not met and/or when used:
   A. In combination with proton pump inhibitors
   B. At doses greater that 200 mg daily

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

III. Belumosudil (Rezurock) is considered investigational when used for all other conditions, including but not limited to:
   A. Systemic sclerosis
   B. Plaque psoriasis
   C. Acute graft-versus-host disease
   D. Graft-versus-host disease in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi)

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 positive treatment response (e.g., stability or reduction in symptoms associated with GVHD: gastrointestinal, ophthalmic, cutaneous, pulmonary); **AND**
IV. Not used in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi); **AND**
V. Proton pump inhibitor therapy (e.g., omeprazole, pantoprazole, lansoprazole, esomeprazole) will not be used in combination with belumosudil (Rezurock).

Supporting Evidence

I. Graft-versus-host disease is a complication of allogenic hematopoietic stem 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.
II. 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. Chronic GVHD (cGVHD) is characterized by that in which symptoms arise more than 100 days after transplant. Glucocorticoids are the mainstay therapy; however, for those with glucocorticoid resistant disease, participation in clinical trials is recommended, or use of tacrolimus, cyclosporine, extracorporeal photopheresis, mycophenolate, rituximab, etanercept (Enbrel), everolimus, sirolimus and others may be considered as second-line therapy. There is lack of consensus on standard second-line therapy given limited or lack of sufficient safety and efficacy data from clinical trials to support use; however, given the poor data available to support any therapy for the treatment of cGVHD, and the established safety profiles of other therapies in this space – utilization of belumosudil (Rezurock) is limited to those that have tried and failed at least two other lines of systemic therapy. This follows the FDA-labeled diagnosis.
III. Other therapies used for the treatment of cGVHD include ibrutinib (Imbruvica) and ruxolitinib (Jakafi) which are indicated in the second-line setting or beyond; however, are often used as later line therapy given safety concerns, cost, and recent approval for this condition. As of

August 2021, guidelines did not specifically recommend any of these therapies over another in the second-line setting or beyond. Given lack of standard of care therapy, safety concerns with drug therapy, and specialized monitoring required for treatment, prescribing by, or in consultation with, a specialist is required.

IV. Use of belumosudil (Rezurock) in combination with other specialty therapies such as ibrutinib (Imbruvica) or ruxolitinib (Jakafi) has not been evaluated for safety and efficacy. Given the safety risks of ibrutinib (Imbruvica) and ruxolitinib (Jakafi), the largely unknown safety profile of belumosudil (Rezurock), as well as lack of data that combination use would provide additional benefit, use of belumosudil (Rezurock) is not allowed at this time. In clinical trials, belumosudil (Rezurock) was evaluated in combination with corticosteroids and calcineurin inhibitors (e.g., tacrolimus); thus, if adjunctive therapy is warranted, these therapies are recommended in combination given availability of safety data with combination use.

V. Belumosudil (Rezurock) was evaluated in two Phase 2 clinical trials, both uncontrolled and open-label. Patients were ≥ 12 years of age, with persistent cGVHD, at least moderate disease, receiving corticosteroids (CS) or CS + calcineurin inhibitor (CI). Patients failed multiple lines of therapy; thus, a standardized control was not available. Primary outcome: objective response rate (ORR). Secondary outcomes: duration of response (DoR), proportion achieving a clinically significant improvement in Lee Symptom Score (LSS), proportion with a reduction in CS doses, mean change in CS dose, proportion of patients discontinuing CS, failure-free survival (FFS).
    - Phase 2a: 54 patients, three treatment arms of various doses, a median of four organs involved, and median of two prior lines of therapy (up to three).
    - Phase 2b: 132 patients, two treatment arms, a median of four organs involved, median of three prior lines of therapy (up to five). Notable past therapies: 34% had ibrutinib (Imbruvica) therapy, 29% had ruxolitinib (Jakafi).

VI. The Phase 2b trial had two treatment arms: 200 mg once daily and 200 mg twice daily. Given similar safety and efficacy, the FDA evaluated data from the 200 mg once daily treatment arm to support approval; however, efficacy across treatment arms were similar. Additionally, the FDA utilized data out to cycle 7 (of 28-day cycles) as a reasonable timeframe to evaluate medication efficacy. The ORR was 75% in one trial and 50% in the other, and the median DoR was 1.9 months, 70% of patients experienced clinical improvement in LSS, the proportion of patients able to reduce the dose of CS was 65%, 20% of patients were able to discontinue CS, and FFS was 75% at six months and 56% at one year.

VII. Use of belumosudil (Rezurock) has not been evaluated in patients less than 12 years of age, and safety implications associated with treatment are largely unknown; thus, use in patients under 12 years of age should be used with extreme caution. Additionally, should be considered only in those that have exhausted all other appropriate therapies for this age group and where benefits of therapy are largely expected to outweigh the risks.

VIII. The NIH recommends ORR as the primary outcome in trials for GVHD: complete resolution of all disease manifestations or improvement in at least one organ site without other progression. The NIH has indicated a 30% ORR in the third-line setting is considered clinically meaningful, and recommends other patient centered outcomes be measured as well (e.g., QoL). These outcomes are expected to correlate with improvement in disease manifestations, reduction in mortality and patient perceived burden of disease.

IX. Results from two trials exceed NIH recommended thresholds, in a population with limited or no further treatment options; thus, the quality of the data is considered moderate, despite the observational nature of the trials. Consistently high ORR, clinically meaningful improvements in QoL parameters, and reduction in corticosteroids across various populations gives confidence that belumosudil (Rezurock) provides clinical value.

X. Common adverse events: fatigue (38%), diarrhea (33%), nausea (31%), cough (28%), URTI (27%), dyspnea (25%), headache (24%), peripheral edema (23%), vomiting (21%), muscle spasms (20%), LFT changes (24%), pneumonia (8%). There is a warning for embryo-fetal toxicity, and no contraindications to therapy. Determined to be unrelated to drug therapy, death occurred in 13 patients in both trials. Dose interruptions occurred in 11% of patients, and drug discontinuations in 18%. Cytopenias and serious infections are known risks of ibrutinib (Imbruvica) and ruxolitinib (Jakafi), leading to high rates of treatment discontinuation. Belumosudil (Rezurock) has not been associated with these safety concerns to date; however, given the observational nature of the data and small number of patients in the clinical trial, the true safety profile is unknown. Additionally, given lack of control, it is unknown what safety characteristics are due to drug or disease.

XI. Belumosudil (Rezurock) has a significant drug-drug interaction with proton pump inhibitors (PPIs). Examples of these include omeprazole, pantoprazole, lansoprazole, esomeprazole. When used concurrently, the belumosudil (Rezurock) dose needs to be doubled, to 200 mg twice daily compared to the standard 200 mg once daily dosing. This results in double the cost of therapy (up to $31,000) per 30-day supply. Additionally, puts members at risk of increased toxicity with therapy with belumosudil (Rezurock) therapy if PPI adherence is inconsistent or not achieved. Thus, the plan requires members be transitioned off of PPI therapy prior to initiating belumosudil (Rezurock). For members with severe symptoms of GERD or another condition requiring PPI therapy; members and providers may consider dietary and lifestyle modifications, or use of an H2 blocker (e.g., famotidine). Belumosudil (Rezurock) also has drug-drug interactions with strong CYP3A inducers (e.g., rifampicin, phenytoin, St. John's Wort). Quantity exceptions will not be allowed in the setting of drug-drug interactions where other management strategies may be employed (e.g., finishing courses of transient therapies, transitioning to other effective therapies). Additionally, belumosudil (Rezurock) was evaluated at doses greater than 200 mg daily in clinical trials; however, additional benefit/efficacy was not shown. Thus, quantity exceptions will not be allowed if the member is unable to achieve adequate efficacy at the 200 mg daily dose.

Investigational or Not Medically Necessary Uses

I. Belumosudil (Rezurock) used in combination with proton pump inhibitors is considered not medically necessary given that concomitant use doubles the cost of belumosudil (Rezurock) therapy. Given alternative management strategies for conditions warranting use of proton pump inhibitors, this drug-drug interaction should be mitigated in ways aside from doubling the dose of belumosudil (Rezurock). See supporting evidence for details. Additionally, clinical trials evaluated doses of belumosudil (Rezurock) therapy greater than 200 mg daily and there was lack of additional efficacy (with increased safety concerns). Thus, use of belumosudil (Rezurock) treatment at doses greater than 200 mg daily is not indicated.

II. Belumosudil (Rezurock) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Systemic sclerosis
    B. Plaque psoriasis
    C. Acute graft-versus-host disease
    D. Graft-versus-host disease in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi)

References

1. Cutler CS, Lee SJ, Arai S, et al. Belumosudil for chronic graft-versus-host disease (CGVHD) after 2 or more prior lines of therapy: the rockstar study. Blood. Published online July 15, 2021:blood.2021012021.
2. Jagasia M, Lazaryan A, Bachier CR, et al. Rock2 inhibition with belumosudil (Kd025) for the treatment of chronic graft-versus-host disease. J Clin Oncol. 2021;39(17):1888-1898.
3. National Comprehensive Cancer Network. NCCN Guidelines: Hematopoietic Cell Transplantation. V3.2021. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=3&id=1501. Accessed August 6, 2021.
4. Rezurock [Prescribing Information]. Kadmon Pharmaceuticals, LLC. Warrendale, PA. July 2021.
5. Jakafi [Prescribing Information]. Wilmington, DE; Incyte Corporation. May 2019.
6. Jagasia M., Perales M.A, Schroeder M.A., et al. Ruxolitinib for the treatment of steroid-refractory actue GVHD (Reach 1): a multicenter, open-label Phase 2 trial. *Blood*. 2020;135(20):1739-1749.
7. Imbruvica [Prescribing Information}. Horsham, PA; Janssen Biotech, Inc. April 2020.
8. Miklos D., Cutler C.S., Arora M., et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. *Blood*. 2017:30:2243-2250.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2021

Policy Type: PA Pharmacy Coverage Policy: UMP182

Description

Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) is an orally administered adenosine triphosphate-citrate lyase inhibitor, and ezetimibe is an intestinal cholesterol absorption inhibitor.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
bempedoic acid (Nexletol)	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C To reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with established ASCVD or high risk for a CVD event, but without established ASCVD	180 mg tablets	30 tablets/30 days
bempedoic acid/ezetimibe (Nexlizet)		180 mg/10 mg tablets	30 tablets/30 days

Initial Evaluation

I. **Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Therapy is prescribed by, or in consultation with, a provider specializing in lipid management (e.g. cardiology, lipidology, endocrinology); **AND**
   C. Therapy with a maximally tolerated statin for at least an 8-week duration has been ineffective; **AND**

1. The member continues to have an LDL-cholesterol level greater than, or equal to, 70 mg/dL while on maximally tolerated statin therapy; **AND**
2. The member will continue maximally tolerated statin therapy in combination with bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet); **OR**
    i. The member has a history of statin intolerance defined as failure of TWO statin medications due to at least ONE of the following:
        a. CK exceeds 10 times the upper limit of normal
        b. LFTs exceed 3 times the upper limit of normal
        c. Severe rhabdomyolysis leading to hospitalization
        d. Severe muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability; **AND**
3. The member will **not** use bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) in combination with simvastatin (Zocor) >20 mg or pravastatin (Pravachol) >40 mg; **AND**

D. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**

E. The member has a history of **atherosclerotic cardiovascular disease (ASCVD)**; **AND**
1. Documentation of clinical atherosclerotic disease via invasive or non-invasive testing (e.g., stress test, imaging); **OR**
2. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction); **AND**
3. Treatment with a PCSK9 inhibitor (e.g. alirocumab [Praluent]), evolocumab [Repatha]) or icosapent ethyl (Vascepa) has been ineffective, contraindicated, or not tolerated; **OR**

F. The member has a diagnosis of **heterozygous familial hypercholesterolemia (HeFH); AND**
1. Diagnosis is confirmed by one of the following:
    i. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (Definite diagnosis classification) or Dutch Lipid Network criteria (score of at least 8)
    ii. Physical signs of familial hypercholesteremia (e.g., arcus cornealis, tendon xanthomas, xanthelasma)
    iii. Clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; **AND**
2. Treatment with a PCSK9 inhibitor (e.g. alirocumab [Praluent]), evolocumab [Repatha]) or icosapent ethyl (Vascepa) has been ineffective, contraindicated, or tolerated; **OR**

G. The member has a diagnosis of **high risk for a cardiovascular (CVD) event in the absence of established ASCVD; AND**
1. High risk for CVD event is defined as one of the following:
    i. Comorbid diagnosis of Type 1 or Type 2 diabetes mellitus in females age ≥65 years and males age ≥60 years
    ii. Reynolds Risk score >30% over 10 years
    iii. SCORE Risk score >7.5% over 10 years
    iv. ASCVD Risk score ≥20% over 10 years

v. Coronary artery calcium score >400 Agatston units (current or historical)

II. Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) are considered investigational when used for all other conditions, including but not limited to:
   A. Primary prevention of ASCVD in patients who are not at high risk for CVD event
   B. Homozygous familial hypercholesterolemia

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 experienced a decrease from baseline LDL while on therapy or LDL remains stable since previous renewal

Supporting Evidence

I. Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) was primarily studied in patients over the age of 18 with a history of ASCVD, HeFH, or those considered at high risk for CVD events. Bempedoic acid (Nexletol) was also studied in multiple trials in patients that were intolerant to two different statins.
II. Bempedoic acid (Nexletol) has drug-drug interactions with doses of simvastatin >20 mg and pravastatin >40 mg due to the potential for increased risk of myopathy.
III. Statins remain the primary recommended treatment option for both cholesterol reduction and cardiovascular protection according to national guidelines. However, these medications are frequently discontinued due to side effects of myalgia and/or musculoskeletal pain; the reported incidence is 5 to 20%, but incidence of true rhabdomyolysis is much smaller. The ACC Expert Consensus guidelines indicate that statin intolerance is generally defined as unacceptable muscle-related symptoms that resolve with discontinuation of therapy and recur with rechallenge on at least two (and preferably three) statins, preferably ones that are metabolized by different pathways and have different lipophilicity/hydrophilicity, and one of which is prescribed at the lowest approved dose. The majority of patients who experience statin-related muscle pain are able to tolerate statin rechallenge with an alternative statin or dose reduction with the same statin.
IV. **Clinical ASCVD and HeFH**
   - Bempedoic acid (Nexletol) was studied in four randomized, double-blind, placebo-controlled Phase 3 trials, and bempedoic acid/ezetimibe (Nexlizet) was studied in one randomized, double-blind, four-arm, Phase 3 trial, in a total of 4,005 patients.
   - The primary efficacy outcome was change in LDL from baseline to 12 weeks compared to placebo. Bempedoic acid (Nexletol) demonstrated reductions of -18.1% (95% CI -20%, -16.1%), -17.4% (95% CI -21%, -13.9%), -21.4% (95% CI -25.1%, -17.7%), -28.5% (95% CI -34.4%, -22.5%), for the Wisdom, Harmony, Serenity, and Tranquility trials respectively.

- Bempedoic acid/ezetimibe (Nexlizet) demonstrated a reduction in LDL of -38% (95% CI -46.5%, -29.6%) compared to placebo.
- Diagnosis of HeFH can be done using genetic testing or evaluation of clinical signs and symptoms. 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). These clinical criteria can be found in the appendix.
- 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 definite FH clinical syndrome.
- Clinical ASCVD is commonly diagnosed based on previous major adverse cardiovascular event (e.g., MI, stroke, stent placement, etc.). However, 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.

V. **MACE Risk Reduction in patients at high risk for CVD Event**

- The safety and efficacy of bempedoic acid (Nexletol) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial in a total of 13,970 adult patients aged 18 to 85 years old who were considered statin intolerant. Enrolled patients had to meet criteria for increased cardiovascular risk, defined as a previous cardiovascular event (secondary prevention) or having clinical features that placed them at high risk for a cardiovascular (CVD) event (primary prevention). Primary prevention patients were required to have one of the following: diabetes mellitus (Type 1 or Type 2) in females age ≥65 years or males age ≥60 years, Reynolds risk score >30% or a SCORE risk score >7.5% over 10 years, or a coronary calcium score >400 Agatston units at any time in the past. At baseline, approximately 70% of the study population were classified as secondary prevention, while 30% were classified as primary prevention.
- The primary endpoint was time-to-first event for a four-component composite of major adverse cardiovascular events (MACE), defined as death from cardiovascular (CV) causes, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization. Key secondary endpoints were assessed in a hierarchical analysis and included a three-component composite of death from cardiovascular causes, nonfatal stroke, or nonfatal MI, fatal or nonfatal MI, coronary revascularization, fatal or nonfatal stroke, death from CV causes, and death from any cause. The primary and first three key secondary endpoints (three-composite MACE, fatal or nonfatal MI, coronary revascularization) were met and considered statistically

significant in favor of bempedoic acid (Nexletol). The results for the other key secondary end points (fatal or nonfatal stroke, death from cardiovascular causes, and death from any cause) did not differ significantly between the bempedoic acid group and the placebo group after a median of 40.6 months of follow-up.

- Although it was not reported as a formal endpoint, reduction in LDL-C from baseline was also measured and reported during the clinical trial period. The mean baseline LDL-C was 139mg/dL in both the bempedoic acid and placebo groups. After 6 months of treatment with bempedoic acid, the mean LDL-C was 107 mg/dL, as compared with 136 mg/dL with placebo, for a difference of 29.2 mg/dL; the observed difference in the percent reductions was 21.1 percentage points (95% confidence interval [CI], 20.3 to 21.9) in favor of bempedoic acid. According to trial investigators, the time-averaged reduction in LDL cholesterol level of 22.0 mg per deciliter over the duration of the trial would be expected to lead to the approximate relative reduction in the risk of cardiovascular events that was observed.
- While the Reynolds Risk score and SCORE risk score were the primary cardiovascular risk assessment tools utilized in the clinical trial, they have limited utility in clinical practice in the United States. The ASCVD risk calculator is the most highly utilized cardiovascular risk assessment tool used by health care practitioners in the United States; the ACC defines high risk as a score of ≥20% over a 10-year period.

VI. AHA/ACC, ESC/EAS, AACE, and NLA guidelines have not been updated to include bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) in the treatment of dyslipidemia. Guidelines currently recommend the use of statins, ezetimibe (Zetia), evolocumab (Repatha), alirocumab (Praluent), and icosapent ethyl (Vascepa) due to their evidence for reducing cardiovascular events.

VII. According to the 2022 ACC Expert Consensus guidance on the non-statin therapies in the management of ASCVD risk, bempedoic acid can be considered as a treatment option for patients who are unable to take statins due to side effects and do not have clinical ASCVD. Guidelines note that after intolerance to at least two (preferably three) statins, adult patients without clinical ASCVD, either with diabetes or without diabetes with additional CVD risk factors, may consider first-line therapy with ezetimibe (Zetia), second-line therapy with bile acid sequestrants (BAS) [e.g., cholestyramine, colestipol, etc.], and third-line therapy with bempedoic acid (Nexletol). While bile acid sequestrants are recommended by the guidelines, these agents have numerous drug-drug interactions, which severely limits their utilization in clinical practice. In patients with clinical ASCVD who are statin intolerant, guidelines recommend the use of either ezetimibe (Zetia) or PCSK9-inhibitors as first-line therapy, depending on the patient's clinical scenario, and bempedoic acid and inclisiran as second-line treatment options.

VIII. Ezetimibe (Zetia) is a common, widely utilized add-on therapy to statin therapy and has well-known safety and efficacy. Ezetimibe (Zetia) also has data on cardiovascular outcomes and has evidence for benefit in patients being treated for dyslipidemia.

Investigational or Not Medically Necessary Uses

I. Primary prevention of ASCVD in patients who are not at high risk for CVD event
   A. There is currently no safety or efficacy data to support the use of bempedoic acid in reducing/preventing ASCVD in patients who are not at high risk for CVD event.

II. Homozygous familial hypercholesterolemia
   A. There is currently no safety or efficacy data to support the use of bempedoic acid in patients with homozygous familial hypercholesterolemia.

Appendix

I. **Heterozygous familial hypercholesterolemia: Diagnosis criteria tables**

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 hypercholesterolemia	
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 (191-250 mg/dL)	3
• LDL-C 4.0-4.9 mmol/L (155-190 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	

References

1. Nexletol [Prescribing Information]. Esperion Therapeutics: Ann Arbor, MI. March 2024.
2. Nexletol/Nexlizet [E-Dossier]. Esperion Therapeutics: Ann Arbor, MI. May 2019.
3. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. JAMA. 2019;322(18):1780-1788.
4. Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. N Engl J Med. 2019;380(11):1022-1032.
5. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis. 2018;277:195-203.
6. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. J Am Heart Assoc. 2019;8(7):e011662.
7. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol. 2019;:2047487319864671.
8. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients. N Engl J Med. 2023;388(15):1353-1364. doi:10.1056/NEJMoa2215024
9. Lloyd-Jones DM, Morris PB, et al. 2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies of LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. J Am Coll Cardiol. 2022;80:1266-1418.

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
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors	Heterozygous familial hypercholesterolemia (HeFH)
	Homozygous familial hypercholesterolemia (HoFH)
	Established atherosclerotic cardiovascular disease (ASCVD)
	Non-familial hypercholesterolemia

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication criteria for high risk for a cardiovascular (CVD) event in the absence of established ASCVD; Updated supporting evidence. Updated initial authorization duration from 6 months to 12 months.	05/2024
Updated supporting evidence	12/2020
Policy created	05/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP174

Description

Benralizumab (Fasenra) is a subcutaneously administered monoclonal antibody (IgG1 Kappa) that antagonizes interleukin-5 (IL-5).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
benralizumab (Fasenra)	Asthma (severe)	30 mg/mL autoinjector	**Loading**: 1 autoinjector/28 days for 3 doses **Maintenance**: 1 autoinjector/ 56 days
	Eosinophilic granulomatosis with polyangiitis (EGPA)		1 autoinjector/28 days

Initial Evaluation

I. **Benralizumab (Fasenra)** may be considered medically necessary when the following criteria below are met:

A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, rheumatology, or ENT (ear, nose, throat); **AND**

B. Must not be used in combination with another monoclonal antibody (e.g., dupilumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**

C. A diagnosis of one of the following:

1. **Asthma (severe); AND**

i. Member is six years of age or older**; AND**

ii. Member has **SEVERE** asthma as defined by one of the following:

a. Symptoms throughout the day

b. Nighttime awakenings, often 7x/week

c. SABA (e.g., albuterol, levalbuterol) use for symptom control occurs several times per day

d. Extremely limited normal activities

e. Lung function (percent predicted FEV1) < 60%

f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**

iii. Member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥300 cells/µL within previous 12 months OR ≥150 cells/µL within 6 weeks of dosing; **AND**
iv. 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**
v. Member is currently being treated with:
    a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
        i. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Striverdi}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
    b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**
vi. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of benralizumab (Fasenra), unless contraindicated; **AND**
vii. Treatment with mepolizumab (Nucala) has been ineffective, contraindicated, or not tolerated; **OR**

2. **Eosinophilic Ganulomatosis with Polyangiitis (EGPA); AND**
    i. Member is 18 years of age or older; **AND**
    ii. Member has a confirmed diagnosis of EGPA (aka Churg-Strauss Syndrome) as defined by ALL of the following:
        a. History or presence of asthma; **AND**
        b. Blood eosinophil level 10% or an absolute eosinophil count >1000 cells/mm^3; **AND**
        c. TWO or more of the following:
            i. Histopathologic evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration or eosinophil rich granulomatous inflammation
            ii. Neuropathy
            iii. Pulmonary infiltrates
            iv. Sinonasal abnormalities
            v. Cardiomyopathy
            vi. Glomerulonephritis
            vii. Alveolar hemorrhage
            viii. Palpable purpura
            ix. Antineutrophil Cytoplasmic Antibody (ANCA) positivity; **AND**
    iii. History of ONE of the following:
        a. At least one confirmed EGPA relapse within the past two years
        b. Failure to attain remission following induction treatment with a standard regimen (e.g., high-dose glucocorticoids with or without

immunosuppressive agents [e.g., methotrexate, mycophenolate mofetil, etc.])

c. Recurrence of EGPA symptoms while tapering oral corticosteroid; **AND**

iv. Member has been on stable doses of concomitant oral corticosteroid therapy for at least 4 weeks (i.e., prednisone or prednisolone at a dose of at least 7.5 mg/day); **AND**

v. Physician has assessed baseline disease severity utilizing an objective measure/tool (e.g., Birmingham Vasculitis Activity Score [BVAS], history of asthma symptoms and/or exacerbations duration of remission or rate of relapses, etc.); **AND**

vi. Treatment with mepolizumab (Nucala) has been ineffective, contraindicated, or not tolerated

II. Benralizumab (Fasenra) is considered investigational when used for all other conditions, including but not limited to:

A. Non-severe, non-eosinophilic phenotype asthma
B. Atopic dermatitis
C. Eosinophilic gastritis
D. Exercise-induced asthma
E. Chronic obstructive pulmonary disease (COPD)
F. Hypereosinophilic 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. Must not be used in combination with another monoclonal antibody (e.g., dupilumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**

IV. A diagnosis of one of the following:

- **Asthma (severe); AND**
  i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
  ii. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of benralizumab (Fasenra), unless contraindicated; **OR**
- **Eosinophilic Granulomatosis with Polyangiitis (EGPA); AND**
  i. Member has exhibited improvement or stability of disease symptoms as evidenced in one or more of the following:
    1. Member is in remission [defined as a Birmingham Vasculitis Activity Score (BVAS) score=0 and a prednisone/prednisolone daily dose of ≤ 7.5 mg]
    2. Decrease in maintenance dose of systemic corticosteroids

3. Improvement in BVAS score compared to baseline
4. Improvement in asthma symptoms or asthma exacerbations
5. Improvement in duration of remission or decrease in the rate of relapses.

Supporting Evidence

I. Benralizumab (Fasenra Pen) is indicated as an add-on maintenance treatment for patients six years and older with a diagnosis of severe eosinophilic asthma (SEA) and for patients 18 years and older with a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA).

II. Benralizumab (Fasenra Pen) for self-administration via an autoinjector was established based off two phase III and one phase I trial that was conducted with the primary objective of usability and pharmacokinetic (PK) exposure. These trials demonstrated that the safety and tolerability of benralizumab (Fasenra Pen) was consistent with the established profile of the medication.

III. There is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.

IV. **Asthma (severe)**

- The provider administered benralizumab (Fasenra), was FDA approved in the setting of severe eosinophilic asthma and was evaluated in one 52-week dose ranging exacerbation trial, three confirmatory randomized, double-blind trials, one 12-week lung function trial, and one 48-week pharmacokinetic and pharmacodynamic trial.
    i. The 52- week dose ranging exacerbation trial was a phase 2 randomized, double-blind, placebo-controlled trial. Benralizumab (Fasenra) was administered every 4 weeks for 3 doses followed by every 8 weeks thereafter. In the benralizumab (Fasenra) treatment arm, there was a decrease in annual exacerbation rate with 2, 20, and 100 mg (-12% [80% CI: -51, 18), -34% [80% CI: 6, 54], and -29% [80% CI: 10, 44], respectively).
    ii. The two confirmatory trials were 48 and 52 weeks in duration. The primary outcome was rate of asthma exacerbations in patients with baseline eosinophil counts of ≥300 cells/µL taking both high-dose ICS and LABA. Rates of exacerbation per year in the benralizumab (Fasenra) arm of both trials was 0.74 and 0.73 compared to 1.52 and 1.01 with placebo (Rate Ratio [95% CI: 0.37, 0.64], [95% CI: 0.54, 0.95], respectively).
    iii. The third confirmatory trial was 28 weeks in duration and evaluated the effects of benralizumab (Fasenra) on reducing the use of maintenance oral corticosteroids (OCS). The primary endpoint was percent reduction from baseline of OCS use during weeks 24 to 28. The median percent reduction from baseline in the benralizumab (Fasenra) arm was 75% compared to 25% in placebo (95% CI: 60, 88).
    iv. The 12-week lung function trial measured lung function by the change from baseline FEV_1 at week 12. The benralizumab (Fasenra) arm showed an increase of 0.057 liters compared to -0.016 liters in placebo (p=0.040)
    v. The 48-week, open-label, pharmacokinetic and pharmacodynamic trial (TATE) was conducted in 28 patients ages six to eleven (mean age 9 years; 6-8 years, n=11; 9-11 years n=17; 32% female, White 29%, Asian 32%, Black or African American 29%) with severe asthma, and with an eosinophilic phenotype. PK, PD, and safety profile of benralizumab 10/30 mg in children with severe eosinophilic asthma are consistent with previous reports in adults and adolescents. Both dose/weight groups achieved

near-complete depletion of eosinophils and no new safety signals were identified. The trial was not powered to assess efficacy outcomes.

B. Since severe asthma is associated with difficulty managing symptoms, therapy should be prescribed and managed by a pulmonologist or other specialist with expertise in asthma/lung function.

C. The Global Initiative for Asthma (GINA) 2024 update recommends the addition of respiratory biologics, with respect to their allergic biomarkers, after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium/high dose maintenance ICS-LABA) or Step 5 (add-on LAMA ± high dose maintenance ICS-formoterol) therapy. Other controller options for Step 4 include high dose ICS-LABA, add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5/5R, anti-IgE, anti-IL4Rα, anti-TSLP, azithromycin, or add-on low dose OCS, though guidelines do note to consider side effects.

D. While benralizumab (Fasenra) is approved for use in patients six years of age and older, the self-administered formulation is only approved for use in patients ≥35kg. For those weighing <35kg benralizumab (Fasenra) should be administered by a healthcare provider.

V. **Eosinophilic Granulomatosis with Polyangiitis (EGPA)**

A. Eosinophilic Granulomatosis with Polyangiitis is a rare disease that does not have well defined diagnostic criteria. Expert consensus suggests that diagnosis should consist of objective evidence of vasculitis coupled with clinical considerations; this generally consists of confirming presence of asthma, blood eosinophilia, and other manifestations, such as chronic rhinosinusitis with nasal polyps, lung infiltrates/obstructive airway disease, glomerulonephritis, cardiomyopathy, neuropathy, gastroenteritis, and purpura. Given the complexities of diagnosing this rare disease, evaluation should involve a specialist.

B. The FDA approval of benralizumab (Fasenra) for the treatment of EGPA was based on a randomized, double-blind, active-controlled, noninferiority, Phase 3 clinical trial (MANDARA) evaluating the safety and efficacy of benralizumab (Fasenra) against mepolizumab (Nucala). Patients enrolled in the trial were age 18 years and older with a diagnosis of EGPA confirmed by the presence of asthma, blood eosinophilia, and at least two other characteristics of EGPA. Patients also were required to have a history of relapsed and/or refractory disease, defined as at least one confirmed EGPA relapse in the previous two years, while receiving oral prednisolone (or equivalent) of ≥7.5 mg/day, failure to attain remission within 6 months prior to baseline visit following induction with treatment with a standard regimen administered for at least 3 months, or recurrent of symptoms of EGPA while tapering oral glucocorticoids within 6 months prior to baseline.

C. The primary endpoint was the proportion of patients achieving remission (defined as a BVAS of 0 or an oral glucocorticoid dose of ≤4mg/day) at weeks 36 and 48. The adjusted percentage of patients with remission at weeks 36 and 48 was 59% in the benralizumab (Fasenra) group and 56% in the mepolizumab (Nucala) group (difference, 3 percentage points; 95% confidence interval [CI], –13 to 18; P = 0.73 for superiority). These results demonstrate noninferiority, but not superiority, of benralizumab (Fasenra) to mepolizumab (Nucala), since the lower bound of 95% confidence interval exceeded the predetermined noninferiority threshold of −25 percentage points and the P value for superiority was greater than 0.05.

D. According to the American College of Rheumatology (ACR)/Vasculitis Foundation (VF) treatment guidelines, treatment approach should be stratified based on severity. For patients with severe (organ-threatening) manifestations, cyclophosphamide and high-dose corticosteroids should be used for remission induction in new-onset or relapsing disease. Methotrexate, azathioprine, mepolizumab, or rituximab should be used for maintenance of remission in relapsing disease. For patients with non-severe manifestations, glucocorticoids in combination with immunosuppressant agents (e.g., methotrexate, azathioprine, mycophenolate mofetil), mepolizumab (Nucala), or high-dose glucocorticoids only (for select patients) can be considered for remission induction in new-onset or relapsing disease, while mepolizumab (Nucala) monotherapy is recommended for maintenance of remission in relapsing disease. Systemic corticosteroids may be used in conjunction with other medications in the maintenance setting, although the goal is to taper off steroids completely.

E. The Birmingham Vasculitis Activity Score (BVAS) is a validated, objective tool for assessment of disease activity in patients with many forms of vasculitis, consisting of a list of items from nine organ systems that reflect the typical features of active systemic vasculitis. It provides valid and reliable definitions for remission and response to therapy, as well as flare, and has been widely used in clinical trials, including the MANDARA trial. Baseline BVAS score should be documented prior to initiation of benralizumab (Fasenra) to accurately measure response to therapy upon follow-up.

F. The results of the MANDARA trial demonstrated non-inferiority of benralizumab (Fasenra) compared to mepolizumab (Nucala) for achievement of remission and similar rates of adverse events between the medications during the trial period. Therefore, it is reasonable to conclude that these agents provide a comparable level of safety and efficacy. Thus, pending no contraindication to therapy, preferred formulary therapies should be utilized based on cost-effectiveness.

Investigational or Not Medically Necessary Uses

I. Benralizumab (Fasenra) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
   A. Non-severe, non-eosinophilic phenotype asthma
   B. Atopic dermatitis
   C. Eosinophilic gastritis
   D. Exercise-induced asthma
   E. Hypereosinophilic syndrome
   F. Chronic obstructive pulmonary disease (COPD)
      i. A single phase IIa study compared benralizumab to placebo in patients with COPD and showed there was no difference in rates of exacerbations; therefore, there is insufficient evidence in the safety and efficacy of benralizumab (Fasenra) for use in patients with COPD.

References

1. Fasenra [Prescribing Information]. Wilmington, DE: AstraZeneca LP. Updated September 2024. Accessed October 2024.

2. National Asthma Education and Prevention Program (NAEPP). Guidelines for the diagnosis and management of asthma. Expert Panel Report 3. Bethesda, MD: National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI); August 2007.
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2024Update. Available from: http://www.ginasthma.org. Accessed June 2024.
4. Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma Allergy. 2014; 7: 53–65.
5. Goldman M, Hirsch I, Zangrilli JG, et al. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. Curr Med Res Opin. 2017 Sep;33(9):1605-1613. doi: 10.1080/03007995.2017.1347091. Epub 2017 Jul 19.
6. Wedner HJ, Fujisawa T, Guilbert TW, et al. Benralizumab in children with severe eosinophilic asthma: Pharmacokinetics and long-term safety (TATE study). *Pediatr Allergy Immunol*. 2024;35(3):e14092.
7. Wechsler ME, Nair P, Terrier B, et al. Benralizumab versus Mepolizumab for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med*. 2024;390(10):911-921.
8. Chung SA, Langford CA, Maz M, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis. *Arthritis Rheumatol*. 2021;73(8):1366-1383. doi:10.1002/art.41773.
9. Emmi G, Bettiol A, Gelain E, et al. Evidence-Based Guideline for the diagnosis and management of eosinophilic granulomatosis with polyangiitis. *Nat Rev Rheumatol*. 2023;19(6):378-393. doi:10.1038/s41584-023-00958-w.
10. Hellmich B, Sanchez-Alamo B, Schirmer JH, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. *Ann Rheum Dis*. 2024;83(1):30-47. Published 2024 Jan 2. doi:10.1136/ard-2022-223764.

Related Policies

Policy Name	Disease state
dupilumab (Dupixent)	Asthma (moderate to severe)
	Atopic dermatitis
	Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
	Prurigo Nodularis
	Eosinophilic Esophagitis
	Chronic Obstructive Pulmonary Disease (COPD)
mepolizumab (Nucala)	Asthma (severe)
	Eosinophilic Granulomatosis with Polyangiitis (EGPA)
	Hypereosinophilic Syndrome
	Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
omalizumab (Xolair)	Chronic Idiopathic Urticaria (CIU)
	Allergic Asthma
	Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
	IgE-Mediated Food Allergy
	Systemic Mastocytosis
reslizumab (Cinqair)	Asthma (severe)
tepezelumab (Tezspire)	Severe Asthma

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to include newly approved eosinophilic granulomatosis with polyangiitis (EGPA) indication	12/2024
Updated policy name to "benralizumab (Fasenra®) as label does not use Fasenra Pen™ to identify the product. Updated QL table to updated standard format. Updated provider administered agents table to include new 10mg/0.5mL dosage form for pediatric patients under 35kg. Updated age criteria and supporting evidence to include the TATE trial for use in pediatric patients six and older. Updated supporting evidence to include GINA 2024 recommendations for the treatment of severe asthma.	7/2024
Updated renewal length of authorization from six months to 12 months. Revised "severe eosinophilic asthma" verbiage "asthma (severe)" in attempts to align with other respiratory biologics policies. For initial	03/2021

criteria: added dupilumab as an example for another monoclonal antibody that must not be used in combination; added prescribed by or in consultation with a specialist requirement; added member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥300 cells/µL within previous 12 months as an "OR" option to existing required ≥150 cells/µL within 6 weeks of dosing; revised verbiage for add-on maintenance treatment requirements to medium- to high-dose, or maximally tolerated ICS and one additional asthma controller medication OR maximally tolerated ICS/LABA combination, added requirement of continued use with background controller medications. For renewal criteria: added "must not be used in combination with another monoclonal antibody"; consolidated list of clinical improvement examples; added continued background controller medications. For supporting evidence: added GINA 2020 guideline recommendations. For investigational or not medically necessary uses: updated verbiage to current policy format.	
Policy created	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP305

Description

Berdazimer (Zelsuvmi) is a nitric oxide (NO) releasing agent.

Length of Authorization

- Initial: Three months
- Renewal: Not eligible/cannot be renewed

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
berdazimer (Zelsuvmi)	Molluscum contagiosum (MC) infection	10.3% Gel	31 g/30 days

Initial Evaluation

I. **Berdazimer (Zelsuvmi)** may be considered medically necessary when the following criteria are met:
   A. Member is one year of age or older; **AND**
   B. Not used in combination with other interventions used to treat Molluscum contagiosum (MC); **AND**
   C. A diagnosis of **Molluscum contagiosum** when the following are met:
      1. Provider attestation that the member meets one of the following:
         i. Extremely bothersome itching or pain
         ii. Concomitant secondary infection or atopic dermatitis
         iii. Affected areas pose a high risk for disease spread and are not coverable with clothing or bandages; **AND**
      2. Treatment with at least two of the following conventional therapies have been ineffective or not tolerated, or all are contraindicated:
         i. podofilox 0.5% solution
         ii. tretinoin 0.05% cream
         iii. Over-the-counter (OTC) therapies (potassium hydroxide solution, salicylic acid, povidone-iodine)

II. Berdazimer (Zelsuvmi) is considered investigational when used for all other conditions, including but not limited to:
   A. Dermatitis not associated with Molluscum contagiosum
   B. Genital warts
   C. Tinea pedis

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Supporting Evidence

I. Molluscum contagiosum (MC) is a highly contagious, predominantly pediatric, skin infection caused by the molluscipoxvirus. It is common, affecting approximately six million people annually in the U.S. and is spread via skin to skin or contact with contaminated items. Molluscum contagiosum (MC) manifests as small, raised lesions that are usually skin colored with an umbilication. Lesions may become itchy, sore, red, or swollen. Atopic dermatitis is a common comorbidity which may be exacerbated, sometimes leading to bacterial skin infections. The infection is usually self-limited but may persist for months to years, impacting quality of life and may be associated with discomfort, psychosocial stigma, and scarring.

II. Berdazimer (Zelsuvmi) is FDA approved for use in ages one year and older for the treatment of Molluscum contagiosum. It is administered topically as a thin layer once daily for up to 12 weeks and intended to be used as monotherapy. Berdazimer (Zelsuvmi) has not been adequately studied in infants younger than one year of age or in combination with other therapies for the treatment of MC, therefore, there's insufficient safety and efficacy data to support such use at this time.

III. Berdazimer (Zelsuvmi) was studied in three Phase 3, multicenter, randomized, double-blind, vehicle-controlled trials in patients with MC. The primary efficacy outcome was the percentage of patients who achieved complete clearance of all treatable MC lesions at week 12. In the B-SIMPLE4 trial, 32.4% of patients in the berdazimer (Zelsuvmi) group achieved complete clearance at week 12 as compared to 19.7% in the vehicle group, representing a treatment difference of 12.7%. The B-SIMPLE1 and B-SIMPLE2 trials also showed a positive treatment effect, favoring berdazimer (Zelsuvmi) but treatment differences against the vehicle gel were not statistically significant. The most common adverse effects reported were mild to moderate application site reactions and include pain (18.7%), erythema (11.7%), pruritus (5.7%), exfoliation (5%), and dermatitis (4.9%). The overall confidence that the product provides a meaningful benefit relative to comparable treatment options is low due to lack of statistically significant findings in two out of the three clinical trials and modest efficacy seen in one trial (B-SIMPLE4) with statistically significant results.

IV. There are currently no clinical practice guidelines for the management of MC. The American Academy of Dermatology Association (AAD) suggests treatment should be initiated when the patient is immunocompromised, has genital area involvement, has a comorbidity of atopic dermatitis, or has extremely bothersome symptoms. The goals of therapy are to alleviate discomfort such as itching, limit transmission to close contacts, and prevent secondary infections.

V. The Centers for Disease Control and Prevention (CDC) notes several topical treatment options including podophyllotoxin, potassium hydroxide, tretinoin, salicylic acid, and iodine, which are self-administered. Podophyllotoxin is associated with clearance rates of up 92% but its efficacy in children less than 10 years old is not established. Potassium hydroxide 10% is associated with clearance rates ranging from 55% to 86% but may be associated with stinging, burning, and pigmentation. When compared to potassium hydroxide, tretinoin also has efficacy in reducing the number of MC lesions with less side effects but with a slower response. Salicylic acid and iodine also show some efficacy with minor side effects. The evidence for other therapies including imiquimod and cimetidine is inconclusive. Treatment with berdazimer (Zelsuvmi) may be medically necessary when standard therapies have been ineffective, not tolerated, or all contraindicated. Engagement with at least two of the following therapies is required: podofilox, tretinoin, or OTC ailments (e.g., potassium hydroxide), as these agents represent highly effective

and safe lower cost alternatives supported by years of clinical practice experience as well as recommendations by the CDC and the AAD.

VI. Berdazimer (Zelsuvmi) is not eligible for renewal because use of berdazimer (Zelsuvmi) beyond 12 weeks of treatment has not been adequately studied, therefore, efficacy and safety beyond 12 weeks is not established. An authorization for a distinct engagement with therapy, such as for a new infection, may be allowed if initial criteria is met.

Investigational or Not Medically Necessary Uses

I. Berdazimer (Zelsuvmi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Dermatitis not associated with Molluscum contagiosum
   B. Genital warts
   C. Tinea pedis

References

1. Zelsuvmi. Package Insert. EPIH SPV, LLC. January 2024.
2. Berdazimer (Zelsuvmi) Product Dossier. Novan. February 2024.
3. Browning JC, Enloe C, Cartwright M, et al. Efficacy and Safety of Topical Nitric Oxide-Releasing Berdazimer Gel in Patients With Molluscum Contagiosum: A Phase 3 Randomized Clinical Trial. *JAMA Dermatol*. 2022;158(8):871-878. doi:10.1001/jamadermatol.2022.2721
4. American Academy of Dermatology Association. Molluscum Contagiosum: Diagnosis and Treatment. November 2023. Accessed on May 20, 2024. Molluscum contagiosum: Diagnosis and treatment (aad.org)
5. Centers for Disease Control. Clinical Overview of Molluscum Contagiosum. Cdc.gov. Updated on May 13, 2024. Accessed on May 20, 2024. https://www.cdc.gov/molluscum-contagiosum/hcp/clinical-overview/index.html
6. Chao YC, Ko MJ, Tsai WC, Hsu LY, Wu HY. Comparative efficacy of treatments for molluscum contagiosum: A systematic review and network meta-analysis. *J Dtsch Dermatol Ges*. 2023;21(6):587-597. doi:10.1111/ddg.15063
7. Syed TA, Lundin S, Ahmad M. Topical 0.3% and 0.5% podophyllotoxin cream for self-treatment of molluscum contagiosum in males. A placebo-controlled, double-blind study. *Dermatology*. 1994;189(1):65-68. doi:10.1159/000246787
8. Rajouria EA, Amatya A, Karn D. Comparative study of 5 % potassium hydroxide solution versus 0.05% tretinoin cream for Molluscum Contagiosum in children. *Kathmandu Univ Med J (KUMJ)*. 2011;9(36):291-294. doi:10.3126/kumj.v9i4.6347
9. Giner-Soriano M, Teixidó C, Marsal JR, et al. Randomized placebo-controlled clinical trial on efficacy and safety of topical 10% Potassium hydroxide for *molluscum contagiosum* treatment in children. *J Dermatolog Treat*. 2019;30(8):750-756. doi:10.1080/09546634.2019.1573305
10. Teixidó C, Díez O, Marsal JR, et al. Efficacy and safety of topical application of 15% and 10% potassium hydroxide for the treatment of Molluscum contagiosum. *Pediatr Dermatol*. 2018;35(3):336-342. doi:10.1111/pde.13438
11. Qureshi A, Zeb M, Jalal-Ud-Din M, Sheikh ZI, Alam MA, Anwar SA. Comparison Of Efficacy Of 10% Potassium Hydroxide Solution Versus Cryotherapy In Treatment Of Molluscum Contagiosum. *J Ayub Med Coll Abbottabad*. 2016;28(2):382-385.
12. Short KA, Fuller LC, Higgins EM. Double-blind, randomized, placebo-controlled trial of the use of topical 10% potassium hydroxide solution in the treatment of molluscum contagiosum. *Pediatr Dermatol*. 2006;23(3):279-281. doi:10.1111/j.1525-1470.2006.00235.x
13. Handjani F, Behazin E, Sadati MS. Comparison of 10% potassium hydroxide solution versus cryotherapy in the treatment of molluscum contagiosum: an open randomized clinical trial. *J Dermatolog Treat*. 2014;25(3):249-250. doi:10.3109/09546634.2013.832135
14. Hanna D, Hatami A, Powell J, et al. A prospective randomized trial comparing the efficacy and adverse effects of four recognized treatments of molluscum contagiosum in children. *Pediatr Dermatol*. 2006;23(6):574-579. doi:10.1111/j.1525-1470.2006.00313.x

15. Leslie KS, Dootson G, Sterling JC. Topical salicylic acid gel as a treatment for molluscum contagiosum in children. *J Dermatolog Treat*. 2005;16(5-6):336-340. doi:10.1080/09546630500430521
16. Capriotti K, Stewart K, Pelletier J, Capriotti J. Molluscum Contagiosum Treated with Dilute Povidone-Iodine: A Series of Cases. J Clin Aesthet Dermatol. 2017;10(3):41-45.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP115

Split Fill Management (Only Applies to bexarotene (Targretin) capsule)*

Description

Bexarotene (Targretin) is an orally and topically administered retinoid that binds to and activates retinoid X receptor subtypes to inhibit growth and induce the regression of tumor cells.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
bexarotene (generic Targretin)	Primary cutaneous T-cell lymphoma, refractory to one prior systemic therapy	75 mg capsule	Based on body surface area calculation, dose to be rounded to the nearest 75 mg
bexarotene (Targretin)		75 mg capsule	
bexarotene gel (generic Targretin)	Primary cutaneous T-cell lymphoma, refractory to one prior therapy	1% topical gel/jelly	60 grams/30 days
bexarotene gel (Targretin)		1% topical gel/jelly	60 grams/30 days

Initial Evaluation

I. **Bexarotene (Targretin)** 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. Bexarotene (Targretin) will **not** be used in combination with mechlorethamine (Valchlor);; **AND**
   D. If the member is a woman of child-bearing potential, the prescriber attests the member has had a negative pregnancy test prior to starting therapy; **AND**
   E. A diagnosis of **primary cutaneous T-cell lymphoma** (e.g., mycosis fungosides, Sezary Syndrome) when the following are met:
      1. For the request of **bexarotene capsules or liquid capsules**;
         i. The member is relapsed and/or refractory to one prior systemic therapy (e.g., oral retinoids, interferon, methotrexate, cyclophosphamide, chemotherapy); **AND**

ii. The request is for <u>generic</u> bexarotene capsules or liquid capsules, unless generic bexarotene has been ineffective or contraindicated; **AND**
iii. A body surface area that has been documented utilizing weight recorded in the past three months ; **AND**
iv. The dose prescribed does not exceed 300 mg/m2/day for at least eight weeks before dose escalation to a maximum of 400 mg/m2/day; **OR**

2. For the request of **bexarotene (Targretin) topical gel/jelly**;
   i. The member has stage IA or IB disease (i.e., limited/localized skin involvement); **AND**
   ii. The member has had a relapse, refractory of, or intolerance to at least two other skin-directed therapies (e.g., mechlorethamine, corticosteroids, phototherapy, imiquimod, topical retinoids); **AND**
   iii. The request is for generic bexarotene gel, unless generic bexarotene gel has been ineffective or contraindicated

II. Bexarotene (Targretin) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Breast cancer
   B. Lung cancer
   C. Gastroesophageal cancers
   D. Acute myeloid leukemia
   E. Non-Hodgkin Lymphoma
   F. Thyroid cancer
   G. Aids-related Kaposi's sarcoma
   H. Alzheimer's disease
   I. Schizophrenia

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 therapy as evidenced by an improvement in CAILS score **<u>or</u>** a decrease in affected surface area, plaque/scale elevation, or severity; **AND**
IV. For **bexarotene capsules or liquid capsules**:
   A. A body surface area that has been documented utilizing weight recorded in the past three months; **AND**
   B. The dose will not exceed 400 mg/m2/day; **AND**
   C. The request is for generic bexarotene capsules or liquid capsules, unless generic bexarotene has been ineffective or contraindicated; **OR**
V. For **bexarotene (Targretin) gel/jelly**:

A. The request is for generic bexarotene gel, unless generic bexarotene gel has been ineffective or contraindicated

Supporting Evidence

I. Bexarotene (Targretin) gel was evaluated in an open-label, Phase I-II trial for the treatment of early stage (IA-IIA) cutaneous T-cell lymphoma in those that were refractory, intolerant to, or reached plateaued response to two prior therapies. Tumor response was assessed via the Composite Assessment of Index Lesion Disease Severity, and was based on a summation of the grades for index lesions, erythema, scaling, plaque elevation, hypo or hyperpigmentation, and area of involvement. Partial response was defined as improvement of at least 50% of the index lesions and did not require confirmation by biopsy. The primary outcome was overall response rate, which occurred in 26% (CI 15%, 40%) of subjects. There was no response seen in those that had stage II disease; thus, the FDA-approval was granted to stage IA/IB only. Additionally, due to the single-arm, open-label trial design, results should be interpreted with caution.

II. Bexarotene (Targretin) capsules were evaluated as systemic therapy in 152 subjects, with advanced and early stage cutaneous T-cell lymphoma in two, open-label trials. Those with advanced disease had been treated with at least one prior systemic therapy, but with a median of two, and up to six therapies. Early disease subjects were intolerant to, were refractory to, or reached plateaued response to two prior therapies. Therapy was initiated at a starting dose of 650 mg/m2/day, with a dose reduction to 500 mg/m2/day; however, neither was tolerated in the study population. The dose was further reduced to 300 mg/m2/day with a dose increase to 400 mg/m2/day if no response was see after eight weeks of therapy. Tumor response was assessed by observation using Composite Assessment of Index Lesion Disease Severity. The endpoint was based on a summation of the grades, erythema, scaling, plaque elevation, hypo or hyperpigmentation and area of involvement. Presence or absence of cutaneous tumors and extra cutaneous manifestations was considered in the response assessment. Tumor responses required confirmation over at least two assessments separated by at least four weeks and partial response was defined as improvement of at least 50% in the index lesions without worsening or development of new cutaneous tumors or non-cutaneous manifestations. At the initial dose of 300 mg/m2/day, one subject had complete clinical tumor response, and 30% (19/62) had partial response. Median duration of tumor response had not been reached by the end of the study. Reponses may be seen as early as four weeks. Due to the single-arm, open-label trial design, results should be interpreted with caution.

III. Commonly utilized skin-directed therapies for cutaneous T-cell lymphoma (e.g., mycosis fungosides, Sezary Syndrome) include the following: topical corticosteroids, topical mechlorethamine (nitrogen mustard), local radiation, topical retinoids (tazarotene, bexarotene), phototherapy, imiquimod, and topical carmustine.

IV. Commonly utilized systemic therapies for cutaneous T-cell lymphoma include the following: brentuximab vedotin, bexarotene, interferons, methotrexate, mogamulizumab, romidepsin, vorinostat, gemcitabine, doxorubicin, and pralatrexate.

V. The cost of one 60-gram tube of topical bexarotene (Targretin) is approximately $30,500; therefore, a quantity limit of one tube per 30-day supply is in place to ensure appropriate use without waste. Should a quantity exception be requested, clinical consideration will be taken to

the amount of body surface area the medication is being applied, rate of application, and amount utilized with administration.

Investigational or Not Medically Necessary Uses

I. Bexarotene (Targretin) has not been sufficiently evaluated and/or is currently in clinical trials for the following indications:
   A. Breast cancer
   B. Lung cancer
   C. Gastroesophageal cancer
   D. Acute myeloid leukemia
   E. Non-Hodgkin Lymphoma
   F. Thyroid cancer
   G. Aids-related Kaposi's sarcoma
   H. Alzheimer's disease
   I. Schizophrenia

** 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. Brenaman D., Duvic M., Kuzel T., et al. Phase 1 and 2 trial of bexarotene gel for skin directed treatment of patients with cutaneous T cell lymphoma. Arch Dermatol 2002; 138:325-332.
2. Heald P., Mehlmauer M., Martin AG., et al. Topical bexarotene therapy for patients with refractory or persistent early stage cutaneous T cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003; 49:801-815.
3. Duvic M., Martin AG., Kim Y., et al, Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001; 137:581-593.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include generic bexarotene gel (generic Targretin); added trial and failure of generic bexarotene gel (generic Targretin) prior to use of the branded product	06/2022
Prior authorization criteria transitioned to policy format, age edit added, updated specialist prescriber requirement to new format, removal of liver function test monitoring requirements. Addition of topical bexarotene (Targretin) to the policy. Initial approval criteria increased from six to 12 months.	11/2019
Previous Reviews	08/2008; 10/2008; 07/2012; 09/2012; 12/2012; 11/2019

birch triterpenes (Filsuvez®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP300

Description

Birch triterpenes (Filsuvez) is a topical gel made from an extract of birch tree bark.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
birch triterpenes (Filsuvez)	Epidermolysis bullosa (EB)	10% (w/w) gel	702 grams/30 days

Initial Evaluation

I. **Birch triterpenes (Filsuvez)** may be considered medically necessary when the following criteria are met:
   A. Member is six months of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a geneticist or dermatologist that specializes in epidermolysis bullosa (EB) management; **AND**
   C. Medication will not be used in combination with beremagene geperpavec (Vyjuvek); **AND**
   D. A diagnosis of **epidermolysis bullosa (EB)** when the following are met:
      1. Provider attestation of genetic mutation for junctional epidermolysis bullosa (JEB) or dystrophic epidermolysis bullosa (DEB), (e.g., *COL17A1*, *LAMB*); **AND**
      2. Provider attestation that documentation of size, length, depth of target wound has been recorded at baseline; **AND**
      3. Provider attestation to all of the following:
         i. Target wounds are free from infection; **AND**
         ii. Member is receiving standard of care preventative or treatment therapies for wound care (e.g., polymeric membrane, superabsorbent dressings, soft-silicone foam)

II. Birch triterpenes (Filsuvez) is considered investigational when used for all other conditions, including but not limited to:
   A. Treatment of epidermolysis bullosa simplex (EBS) wounds
   B. Treatment of Kindler syndrome wounds (KEB)

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**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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 is not used in combination with beremagene geperpavec (Vyjuvek); **AND**
IV. Member has exhibited improvement or stability of disease symptoms [e.g., closure of wounds, decrease in size of wounds, decrease in pain or itch]

Supporting Evidence

I. Birch triterpenes (Filsuvez) is FDA-approved in those six months of age and older for the treatment of junctional epidermolysis bullosa (JEB) and dystrophic epidermolysis bullosa (DEB).
II. As epidermolysis bullosa (EB) is a complex skin disease, it is recommended that patients receive care from a geneticist or dermatologist who specializes in EB, or at least in consultation with one. There are about 35 centers that specialize in EB over the nation; therefore, all patients should be seen in person at least yearly at one of these centers and can continue follow up visits at localized primary care providers or specialists.
III. Epidermolysis bullosa is a rare, inherited connective tissue disorder that causes abnormalities in the structures that hold the skin together, resulting in blisters, non-healing ulceration, scars, and eventually fibrosis of the skin in response to friction or trauma. In severe forms of the disease, even the friction from clothes rubbing against the skin can trigger these reactions. Epidermolysis bullosa also has manifestations beyond the skin, such as blistering, ulcerations, and scarring in the lining of the gastrointestinal and respiratory tracks. Fusion of fingers and toes can occur with loss of limb function and the risk of squamous cell skin carcinoma is quite high.
IV. Depending on the type of EB a patient has, symptoms and life expectancy can vary greatly. Epidermolysis bullosa should be considered in any neonate who presents with blisters and/or erosions in the absence of another plausible etiology (e.g., infection). Blistering or skin fragility may develop later in infancy or childhood, particularly related to diaper changing or crawling, and even in adulthood in milder EB subtypes. Clinical overlap of symptoms can make it difficult to distinguish between subtypes of EB, so genetic testing is important to confirm a diagnosis. A skin biopsy is usually the first step for newly suspected EB, followed by genetic testing to confirm the exact EB subtype diagnosis which is crucial for managing long term outcomes with EB. Currently, Dystrophic EB Research Association (DEBRA) (the internal EB center with a US chapter) offers free genetic testing for any suspected patients.
V. Treatment of EB is largely supportive and includes wound care, control of infection, nutritional support, and prevention and treatment of complications. Care plans for patients with EB should be individualized according to age, severity, symptoms, complications, and patient priorities. The 2017 International Consensus from DEBRA (Dystrophic EB Research Association) gives detailed recommendations for all aspects of EB care and helpful advice for caregivers. Recommendations for skin and wound care include bathing in saline water and using appropriate bandage or dressing types such as silicone and foam dressings. In May 2023, a gene therapy called beremagene geperpavec (Vyjuvek) was approved for use in patients with DEB only to promote wound healing by expressing collagen. In December 2023, birch triterpenes (Filsuvez) received approval in DEB and JEB patients to assist with wound closure in these patients.

VI. The safety and efficacy of birch triterpenes (Filsuvez) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial (EASE). During the 90-day trial, patients of at least 21 days of age (n=223) with DEB, JEB, or Kindler EB (KEB) were randomized 1:1 to receive birch triterpenes (n=109) or the control gel (n=114). No patients with KEB were enrolled. Patients were not allowed to receive systemic antibiotics or have chronic wounds (wounds present over three weeks) older than nine months of age or that were infected. All wounds were treated at least every four days with application to the wound or the dressing at each change with one target wound was designated as being measured for the primary endpoint. This wound was defined as an EB partial-thickness wound, involving both the epidermis and the dermis layers of the skin, of 10 cm^2 to 50 cm^2 in size; if multiple wounds met this description, the wound of the largest size, maximum depth, and oldest was chosen. The primary endpoint was the number of patients with first complete closure of the EB target wound, within 45 (± seven days) of treatment.

Primary Outcome	Birch Triterpenes (n=109)	Control Gel (n=114)
Proportion of patients (%) with first complete closure of EB target wound within day 45	41.3	28.9
	Risk Ratio: 1.44 (95% CI: 1.01, 2.05, *p=0.013*)	

VII. While the primary endpoint was statistically significant, the subgroup analysis was only significant in those with recessive DEB as this was the largest group reflected in the study patient population. Secondary endpoints were time to first complete closure of the EB target wound and proportion of patients with first target wound closure in 90 days (± seven days), incidence and severity of wound infections, procedural pain scores, and patient quality of life measurements. While all of these trended to favor birch triterpenes (Filsuvez), none reached a statistically significant difference. A post-hoc analysis did show statistical significance in the weekly frequency of dressing changes for birch triterpenes (Filsuvez) with there being three fewer changes every two weeks versus placebo.

VIII. Overall, the quality of evidence is moderate. Complete wound closure represents a clinically meaningful outcome and substantially more patients treated with birch triterpenes (Filsuvez) were able to achieve this endpoint vs control gel. Secondary endpoints also favored birch triterpenes (Filsuvez) and while not statistically significant, all showed positive trends in treating those with EB.

IX. Birch triterpenes (Filsuvez) is available as a 23.4-gram sterile tube, each tube to be used as single use for one wound dressing change applied as one millimeter per wound. Multiple wounds can be treated with each tube. Quantity limit of one tube per day is set based on the average amount used in the clinical trial as well as practical knowledge about the frequency of wound dressing changes by caregivers, which can occur daily. The monthly quantity required will depend on the on the surface area being treated and is expected to vary from patient to patient. Quantity exceptions may be allowed if the medical necessity for higher quantity is supported by documentation from the treating physician.

Investigational or Not Medically Necessary Uses

I. Birch triterpenes (Filsuvez) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Treatment of epidermolysis bullosa simplex (EBS) wounds
   B. Treatment of Kindler syndrome wounds (KEB)

References

1. Filsuvez. Package Insert. Lichtenheldt GmbH; December 2023.
2. Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Oleogel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. Br J Dermatol. 2023;188(1):12-21.
3. Denyer J, Pillay E, Clapham J. Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus. Wounds International, 2017.
4. Birch triterpenes preapproval product dossier. Chiesi Pharmaceuticals. December 2023.
5. Chiesi USA. Clinical outreach. February 29, 2024.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2024

bosutinib (Bosulif®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP116

Split Fill Management*

Description

Bosutinib (Bosulif) is a tyrosine kinase inhibitor that inhibits the Bcr-Abl kinase which promotes chronic myelogenous leukemia (CML). It is also known to inhibit Src-family kinases including Src, Lyn, and Hck.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
bosutinib (Bosulif)	100 mg tablets	CML, newly diagnosed chronic phase; CML, resistant or intolerant to prior therapy	90 tablets/30 days
	400 mg tablets		30 tablets/30 days
	500 mg tablets		30 tablets/30 days
	50 mg capsules		90 tablets/30 days
	100 mg capsules		30 tablets/30 days

Initial Evaluation

I. Bosutinib (Bosulif) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
   C. A diagnosis of **chronic myelogenous leukemia (CML)** when the following are met:
      1. Newly diagnosed chronic phase Philadelphia chromosome-positive (Ph+) CML; **OR**
      2. Chronic, accelerated, or blast phase Ph+ CML; **AND**
         i. Resistant or intolerant to prior treatment with a tyrosine kinase inhibitor [e.g. imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna)]

II. Bosutinib (Bosulif) is considered investigational when used for all other conditions, including but not limited to:
   A. Glioblastoma
   B. Dementia
   C. Non-small cell lung cancer
   D. Mesothelioma
   E. Bladder cancer
   F. Ovarian, peritoneal, uterine cervical cancer

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G. Thymoma
H. Thymus 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. The medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
V. Documentation of response to treatment, defined by the stabilization of disease or a decrease in tumor size or tumor spread.

Supporting Evidence

I. Bosutinib (Bosulif) is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy OR newly diagnosed chronic phase Ph+ CML.
II. Prior therapy may include, but is not limited to, one of the following: imatinib (Gleevec), dasatinib (Sprycel), and/or nilotinib (Tasigna).
III. All TKIs are all highly effective with no differences in overall survival between imatinib and the second generation TKI therapies bosutinib, dasatinib, or imatinib.
IV. Members with primary treatment resistance to imatinib can be treated with any second generation TKI therapy (bosutinib, dasatinib, or nilotinib), while giving consideration to BCR-ABL1 mutation status. The second-generation TKI therapies are active against many mutations resistant to imatinib.
V. Members with primary treatment resistance to bosutinib, dasatinib, or nilotinib may be treated with any alternate TKI other than imatinib and giving consideration for BCR-ABL Mutation status.
VI. Treatment recommendations from NCCN Guidelines - Version 02.2020 CML

THERAPY	CONTRAINDICATED MUTATIONS
Bosutinib	T315I, V299L, G250E, or F317L
Dasatinib	T315I/A, F317L/V/I/C or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I or G250E

VII. Intolerance is defined as progression while taking a TKI, and/or the inability to tolerate the current minimum recommended dose, or inability to dose-increase due to toxicity. Resistance and intolerance to both dasatinib (Sprycel) and nilotinib (Tasigna) are manifested similarly to that of imatinib (Gleevec).
VIII. Disease progression is defined as transformation to accelerated or blast phase, or loss of previously attained response. Treatment was continued until disease progression (transformation to accelerated or blast phase, or loss of previously attained response),

unacceptable toxicity, or withdrawal of consent. Patients were removed from the study if they were unable to tolerate a bosutinib (Bosulif) dose of ≥ 300 mg/d.

Investigational or Not Medically Necessary Uses

I. There is limited to no evidence to support the use of bosutinib (Bosulif) in any other condition.
II. Glioblastoma
    A. Bosutinib (Bosulif) was evaluated in small phase 2 study in adults with recurrent glioblastoma, however the study met pre-specified criteria for early closure due to progression. Bosutinib (Bosulif) monotherapy does not appear to be effective in recurrent glioblastoma.

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References

1. Bosulif [Prescribing Information]. New York, NY. Pfizer labs: October 2019.
2. Facts & Comparisons [Internet database]. Wolters Kluwer Health, Inc. [Cited 2012 September 27]. Available with subscription at: http://online.factsandcomparisons.com
3. Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood. 2011;118(17):4567-76.
4. Taylor JW, Dietrich J, Gerstner ER, et al. Phase 2 study of bosutinib, a Src inhibitor, in adults with recurrent glioblastoma. J Neurooncol. 2015;121(3):557-63.
5. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia – v.2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 50mg and 100mg capsules to QL	2024
Prior authorization criteria transitioned to policy format. Updated requirement of prior therapy to state prior tyrosine kinase inhibitor rather than stating imatinib. Extended renewal duration from four months to 12 months. Required agent be used as monotherapy and not in combination with other oncologic medications.	12/2019
Previous Reviews	02/2013; 01/2018; 12/2018;

Policy Type: PA Pharmacy Coverage Policy: UMP067

Description

Testosterone is the primary endogenous androgen responsible for promoting growth and development of male sex organs and the maintenance of secondary sex characteristics.

Length of Authorization

- Initial:
  - i. **For delayed puberty in males (e.g. constitutional growth delay)**: six months
  - **ii. All other indications**: 12 months
- Renewal:
  - i. **For delayed puberty in males (e.g. constitutional growth delay)**: six months; NOT to exceed 18 months of treatment
  - ii. **All other indications**: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
testosterone (Androderm)	Primary hypogonadism; hypogonadotropic hypogonadism; metastatic breast cancer; delayed puberty (males) (e.g. constitutional growth delay)	2 mg/24 hour patch	60 patches/30 days
		4 mg/24 hour patch	30 patches/30 days
testosterone (Axiron)		30 mg actuation roll-on solution	110 ml/30 days
testosterone (Natesto)		5.5 mg/actuation nasal gel	22 g/30 days
testosterone (Striant)		30 mg buccal system	60 buccal systems/ 30 days
testosterone 1% (AndroGel, Testim, Vogelxo)		25 mg/2.5gm gel	300 g/30 days
		50 mg/5gm gel	300 g/30 days
		12.5 mg/actuation gel pump	300 g/30 days
testosterone 1.62% (AndroGel, Vogelxo)		20.25 mg/ 1.25 gm gel packet	150 g/30 days
		40.5 mg/2.5gm gel packet	150 g/30 days
		20.25 mg/actuation gel pump	150 g/30 days
testosterone 2% (Fortesta)		10mg/ actuation gel	120 g /30 days
testosterone cypionate (Depo-testosterone)		100mg/ mL intramuscular injection	8 mL/28 days
		200mg/ mL intramuscular injection	4 mL/28 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Testosterone enanthate	Primary hypogonadism; hypogonadotropic hypogonadism; metastatic breast cancer; delayed puberty (males) (e.g. constitutional growth delay)	200 mg/mL intramuscular injection	4 mL/28 days
testosterone enanthate (Xyosted)	Primary hypogonadism; hypogonadotropic hypogonadism	50 mg/ 0.5 mL subcutaneous solution autoinjector	5 mL/28 days
		75 mg/0.5 mL subcutaneous solution autoinjector	5 mL/28 days
		100 mg/ 0.5 mL subcutaneous solution autoinjector	4 mL/28 days
testosterone undecanoate (Jatenzo, Tlando, Kyzatrex)	Primary hypogonadism; hypogonadotropic hypogonadism	100 mg capsule	60 capsules/30 days
		150 mg capsule	120 capsules/30 days
		158 mg capsule	120 capsules/30 days
		198 mg capsule	120 capsules/30 days
		200 mg capsule	120 capsules/30 days
		237 mg capsules	60 capsules/30 days
		112.5mg capsules	120 capsules/30 days
methyltestosterone (Methitest)	Primary hypogonadism; hypogonadotropic hypogonadism; metastatic breast cancer; delayed puberty (males) (e.g., constitutional growth delay)	10 mg tablets or capsules	Men: 150 tablets /30 days Women: 600 tablets/30 days

Initial Evaluation

Generic testosterone cypionate injection, generic testosterone enanthate injection, and generic topical testosterone 1% (generic Androgel 1%), and generic topical testosterone 1.62% pump (generic androgel 1.62% pump) are preferred agents.

- There is no prior authorization required on these preferred generic agents, unless

I. **Methyltestosterone (Methitest), testosterone (Androderm, Axiron, Natesto, Striant), testosterone 1% (AndroGel, Testim, Vogelxo), testosterone 1.62% (AndroGel, Vogelxo), testosterone 2% (Fortesta), testosterone cypionate (Depo-testosterone), testosterone enanthate (Xyosted), testosterone undecanoate (Jatenzo, Tlando, Kyzatrex)** may be considered medically necessary when the following criteria are met:

A. A diagnosis of one of the following:

1. **Gender dysphoria; OR**
2. **Delayed puberty in males (e.g. constitutional growth delay); AND**
   i. Age is 14 years or older; **AND**
   ii. Prescribed by, or in consultation with, an endocrinologist; **AND**

iii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
    a. generic testosterone enanthate; **OR**
    b. generic testosterone cypionate; **OR**

3. **Metastatic breast cancer; AND**
    i. Age is 18 years or older; **AND**
    ii. Prescribed by, or in consultation with, an oncologist; **AND**
    iii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
        a. Generic injectable testosterone cypionate; **OR**
        b. Generic injectable testosterone enanthate; **OR**

4. **Primary or Secondary Hypogonadism; AND**
    i. Diagnosis further defined as one of the following:
        a. Primary hypogonadism (testicular failure) due to: Klinefelter syndrome (KS), cryptorchidism, orchiectomy, vanishing testes syndrome, chemotherapy affecting or radiation to the testes, testicular trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome, or myotonic dystrophy; **OR**
        b. Secondary hypogonadism (pituitary-hypothalamic hypogonadism) due to hypothalamic or pituitary tumor, iron overload syndromes, idiopathic hypogonadotropic hypogonadism, hyperprolactinemia, head trauma, pituitary surgery, or radiation; **AND**
    ii. (For adults only) Two sub-normal testosterone concentration levels taken on two separate mornings while fasting; **AND**
    iii. Treatment with all of the following has been ineffective, contraindicated, or not tolerated**:**
        a. Generic injectable testosterone; **AND**
        b. Generic topical testosterone (generic AndroGel)

II. Testosterone is considered not medically necessary when used for all other conditions, including
    A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
    B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
    C. Men with symptoms of hypogonadism, however, present with testosterone level within normal range upon initial presentation.

III. Testosterone is considered investigational when used for all other conditions, including but not limited to:
    A. Age-related hypogonadism in adults
    B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
    C. For the healing of fracture

D. Functional uterine bleed
E. Treatment of weight loss unrelated to HIV-wasting

Renewal Evaluation

I. Member has received a previous prior authorization approval for a brand testosterone or high-cost generic agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member has exhibited improvement or stability of disease symptoms from baseline (e.g., improved mood, decreased fatigue, no or diminished signs of gynecomastia, endogenous testosterone levels increasing after stopping therapy, testes enlargement); **AND**
III. (For Adults Only) One testosterone level within mid-normal range taken within the last 12 months that indicates improvement from baseline levels (pre-treatment); **AND**
IV. If diagnosis of **Delayed puberty (e.g. constitutional growth delay):**
    a. Has NOT had more than 18 months of treatment.

Supporting Evidence

I. Per the 2018 AUA guidelines, diagnosis of hypogonadism should be confirmed prior to initiating testosterone replacement therapy. Testosterone levels should be drawn ideally between 8 and 10 AM while fasting due to the diurnal fluctuation of testosterone and its sensitivity to glucose ingestion. A separate, confirmatory measurement is recommended. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.
II. The Endocrine Society strongly advises against “trial periods” of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.
III. The benefit of increasing testosterone concentration has only been shown in patients with organic hypogonadism due to disorders of the hypothalamus, pituitary or testes.
IV. In patients within normal range, or have low testosterone concentration due to age, obesity, or otherwise, the benefit of increased testosterone has not been shown. Rather, in this patient population with low testosterone and an intact gonadal system, increasing testosterone is associated with an increase of certain health risks, including cardiovascular disease. Due to this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.
V. Lower limit of the normal total testosterone (TT) to the CDC standard in healthy, non-obese young men is 264 ng/dL (9.2 nmol/L).The lower limit of normal range is considered to be <150 ng/dL, with a noted normal range of 200 to 400 ng/dL. For adult patients, it is recommended to confirm low T concentrations as 30% of men will present with a normal T concentration value when measured again.
VI. Testosterone replacement therapy is subject to abuse at doses higher than recommended for approved indications and in combination with other anabolic androgenic steroids. Abuse-related adverse events include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, hepatotoxicity, and serious psychiatric complaints.

VII. Guidelines advise to monitor testosterone levels 3-6 months after initiation of therapy and then annually. Serum testosterone concentrations should be brought into the mid-normal range. Testosterone levels may vary depending on dosage form.

VIII. Boys undergo puberty development around the age of 14. Bone age is delayed by 2 years or more in bone maturation in patients with delayed puberty, though not a diagnostic approach but characteristic of disease. Delayed puberty can be treated with short term hormonal therapy by administering testosterone enanthate or cypionate (50 mg IM once monthly) for six months and then reassess endogenous gonadal function and size six months later. Pubertal development was indicated by testicular enlargement and increasing testosterone concentrations after the cessation of therapy. It is unusual for a boy with delayed puberty to require more than two three- to six-month courses of testosterone therapy before spontaneous puberty occurs.

IX. Pediatric testosterone levels are to be very low or not present as boys may not have functioning testes or without testes. Guidelines recommend testing for other blood tests including LH, FSH, TSH. It is not reasonable nor recommended to require pediatric patients to check multiple blood tests.

X. Generic injectable testosterone is primarily used in delayed puberty due to amount of reliable data available; other formulations or salts have not been studied in patients under the age of 18 and are otherwise not readily recommended.

XI. Use of bone age is indicated as characteristic of delayed puberty, but not an absolute indication. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. X-ray of the hand and wrist to determine bone age should be obtained every six months to assess the effect of treatment on the epiphyseal centers.

XII. Androgens in metastatic breast cancer (women that are 1-5 years postmenopausal advanced inoperable metastatic breast cancer or in premenopausal women who have benefited from oophorectomy with hormone response tumors) is rare, including testosterone use. Androgens were found inferior to high-dose estrogens, even though response rates are high. Additionally, if androgen therapy is required, the preferred formulation is fluoxymesterone.

Investigational or Not Medically Necessary Uses

I. Testosterone products are considered not medically necessary when used for conditions or settings listed below:
   A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
   B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
   C. Men with symptoms of hypogonadism, however, present with testosterone level within normal range upon initial presentation.

II. Testosterone products have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Age-related hypogonadism

i. The role of testosterone replacement to treat the natural decline in serum testosterone common in men over the age of 60, without identified pituitary or hypothalamic disease, is uncertain.

B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
C. For the healing of fracture
D. Functional uterine bleed
E. Treatment of weight loss unrelated to HIV-wasting

References

1. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018; 103:1715.
2. Yeap B, Wu F. Clinical practice update on testosterone therapy for male hypogonadism: Contrasting perspectives to optimize care. Clinical Endocrinology 2019; 56:65. Available at: DOI: 10.1111/cen.13888
3. Jatenzo [Prescribing Information]. Clarus Therapeutics, Inc.: Northbrook, IL. March 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206089s000lbl.pdf
4. Crowley, W. F. (2018, July 23). *Approach to patient with delayed puberty*. Retrieved from UpToDate.
5. Snyder, P. J. (2018, April 21). *Clinical features and diagnosis of male hypogonadism*. Retrieved from UpToDate.
6. Tangpricha, V. (2018, August 22). *Transgender men: Evaluation and management.* Retrieved from UpToDate.
7. Swerdloff, R. A Phase 3, Randomized, Active-controlled, Open-label Study of the Safety and Efficacy of Oral Testosterone Undecanoate (TU) in Hypogonadal Men. Retrieved from: https://clinicaltrials.gov/ct2/show/study/NCT02722278
8. Gould DC, Petty R, Jacobs HS. The male menopause: does it exist? BMJ 2000;320:858-861.
9. National Institute on Aging. Scientific task force to examine usefulness of testosterone replacement therapy in older men. NIH News Release. November 6, 2002. Available at: http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20021106ScientificTask.htm (access date April 4, 2007).
10. Miller KK. Special Articles: Hormones and Reproductive Health. J Clin Endocrinol Metab 2001;86(6):2395-2401.
11. Conway AJ, Handelsman DJ, Lording DW, Stuckey B, Zajac JD. Use, misuse and abuse of androgens. MJA 2000; 172:220-224.
12. The Formulary Monograph Service, Facts and Comparisons, St Louis, Missouri, 2003.
13. Francis S. Greenspan and David G. Gardner eds. Lange Basic and Clinical Endocrinology. 7th ed. McGraw-Hill Companies, Inc.; 2004
14. Lui PY, Swerdloff RS, Wang C. Relative testosterone deficiency in older men: Clinical definition and presentation. Endocrinol Metab Clin N Am. 2005;34:957-72.
15. Adkins D. Child With Suspected Delayed Puberty. Pediatric Endocrine Society. Available at: https://pedsendo.org/wp-content/uploads/2020/09/Child-with-suspected-delayed-puberty-final.pdf
16. Methitest [package insert]. Global Pharmaceuticals. June 2014.
17. Android [package insert]. Valeant Pharmaceuticals North America LLC. July 2014.
18. Testred [package insert]. Valeant Pharmaceuticals North America LLC. June2014.
19. Tlando [package insert]. Antares Pharma, Inc. March 2022.
20. Kyzatrex [package insert]. Marius Pharmaceuticals. July 2022.
21. Ma, C. X. (2022, April 28). *Treatment approach to metastatic hormone receptor-positive, HER2-negative breast cancer: Endocrine therapy and targeted agents.* Retrieved from UpToDate.

Appendix:

I. Testosterone lab monitoring assessment based on dosage form

Dosage Form	Recommendation
Injectable enanthate/cypionate	Adjust dose or frequency if >600 or <350 ng/dL
Transdermal gels	Assess 2-8 hours following application
Transdermal patches	Assess 3-12 hours after application
Buccal bioadhesive tablet	Assess immediately before or after fresh application
Oral undecanoate	Assess 3-5 hours after ingestion with fat-containing meal
Injectable undecanoate	Assess at end of the dosing interval prior to next injection

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated Androgel 1% formulation in QL table to read 12.5 mg/actuation	07/2024
Added new medication Tlando capsules. Added methyltestosterone (Methitest) and accompanying indications. Removed Aveed® as it is HCP administered medication. Updated initial criteria to remove including removal of age requirement and pertinent negative cancer assessments in hypogonadism use. Added renewal criteria. Added criteria for delayed puberty in males and metastatic breast cancer. Updated policy name.	09/2022
Change to policy format; added supplementary evidence section; updated references	07/2018
Add methyltestosterone to policy, remove DDID column from QL section	12/2019
Policy created	06/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP258

Description

Budesonide (Tarpeyo) is an orally administered corticosteroid indicated to reduce the loss of kidney function in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression.

Length of Authorization

- Initial: Ten months
- Renewal: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
budesonide (Tarpeyo)	Primary Immunoglobulin A Nephropathy (IgAN)	4 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Budesonide (Tarpeyo)** 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; **AND**
   C. 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. Member has an eGFR ≥ 35mL/min/1.73 m^2; **AND**
      3. Documentation of elevated protein levels in urine as indicated by proteinuria ≥ 1 g/day or urine protein to creatinine ratio (UPCR) of ≥ 1.5 g/g; **AND**
      4. Member has been optimized on an ACE inhibitor (e.g., lisinopril, benazepril, etc.) or an ARB (e.g., losartan, olmesartan, valsartan, etc.) at a maximum tolerated dose for at least three months; **AND**
      5. Treatment will be used in combination with an ACE inhibitor or ARB; **OR**
         i. Treatment with an ACE inhibitor or ARB has been contraindicated or not tolerated; **AND**
      6. Member has documentation of intolerance or contraindication to generic systemic corticosteroid therapy (e.g., prednisone, prednisolone, methylprednisolone).

II. Budesonide (Tarpeyo) is considered investigational when used for all other conditions, including but not limited to:
   A. IgAN in members less than 18 years of age

B. Secondary IgA Nephropathy
C. Budesonide (Tarpeyo) used in combination with sparsentan (Filspari)
D. Focal segmental glomerulosclerosis (FSGS)
E. Chronic kidney disease (CKD) other than primary IgAN

Renewal Evaluation

I. N/A – Product not eligible for renewal

Supporting Evidence

I. Budesonide (Tarpeyo) is the first therapy FDA approved for the treatment of patients with primary immunoglobulin A (IgA) nephropathy. IgA nephropathy, also known as Berger's disease, is a rare kidney disease that occurs when IgA antibody deposits build up in the kidneys, causing inflammation that damages kidney tissues. The deposits can cause the kidneys to leak blood and protein into the urine. IgA nephropathy complications can include high blood pressure and chronic kidney disease, which can sometimes progress to kidney failure. As such, patients should be managed in consultation with a nephrologist.
II. Clinical studies NEFIGAN and NefIgArd were conducted in adult patient populations (18 years of age and older). The efficacy and safety of budesonide (Tarpeyo) in pediatric populations is unknown at this time. Additionally, guidelines indicate there is insufficient data currently available to recommend that pediatric IgAN populations be managed as adults.
III. Budesonide (Tarpeyo) was studied in a phase 3, multicenter, randomized, double-blind, placebo controlled trial (NefIgArd). The trial consisted of two parts. Part A which included a screening period, 9-month treatment period, with a 3-month follow-up (including a 2-week taper) and part B which consisted of a 15-month observational follow-up period where no treatment was given. The primary endpoint of part A was the ratio of urinary protein-creatinine ratio (UPCR) at 9 months following the first dose of study drug compared to baseline. In part B, the primary endpoint assessed the time-weighted average of change in eGFR from baseline.
    - The trial met the prespecified part A primary endpoint based on an interim analysis of 199 randomized patients who had completed the Month 9 visit. The interim analysis showed a 31% reduction in UPCR in patients treated with budesonide (Tarpeyo) 16 mg once daily compared to placebo (95% CI: 16% to 42% reduction; p=0.0001). In the final analysis of 364 patients, the percentage change in UPCR observed at 9 months was consistent with the results in the subset of 199 patients included in the interim analysis.
    - In the final analysis of 364 patients, the trial met the prespecified part B primary endpoint (p<0.0001). The favorable effect of budesonide (Tarpeyo) on eGFR was seen by Month 3 (the earliest assessment) and did not appear to increase in magnitude over two years. At Year 2, there was a 5.9 mL/min/1.73 m2 difference in the mean change from baseline in eGFR between budesonide (Tarpeyo) and placebo (95% CI: 3.3 to 8.5 mL/min/1.73 m2 ; p<0.0001).
    - The most commonly reported treatment-emergent adverse events during treatment with budesonide (Tarpeyo) were peripheral edema (31 [17%] of 182 patients vs placebo, 7 [4%] of 182 patients), hypertension (22 [12%] vs six [3%]), muscle spasms

(22 [12%] vs 7 [4%] patients), acne (20 [11%] vs 2 [1%]), and headache (19 [10%] vs 14 [8%]).

IV. In clinical studies participants underwent treatment for budesonide (Tarpeyo) for nine months followed by a two-week dose taper. Given treatment is a course of high dose steroid, dose tapering is recommended to avoid steroid withdrawal syndrome.

V. KDIGO guidelines indicate 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.

VI. Reduced glomerular filtration rates can be a marker of kidney disease; specifically, those under 35mL/min/1.73 m^2 which can indicate moderate-to-severe kidney disease (stage 3b). Guidelines recommend supportive care for these patients with moderate-to-severe kidney disease as opposed to therapy with corticosteroids.

VII. The primary focus of IgAN management is optimized supportive care (i.e., blood pressure management, maximally tolerated ACEi/ARBs, lifestyle modification, and reduction of cardiovascular risks). Proteinuria and eGFR are the only validated prognostic serum or urine biomarkers in IgAN. In all types of proteinuric glomerular diseases, including IgAN, higher levels of proteinuria are associated with worse kidney outcomes (acute kidney injury, chronic kidney disease, end stage renal disease, etc.). Reduction in proteinuria, independent of blood pressure control, is associated with improved kidney outcomes. KDIGO guidelines recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB to further protect renal function.

VIII. Patients with IgAN who are at high risk of progressive chronic kidney disease (CKD) despite maximal supportive care are defined as those with proteinuria greater than 0.75 to 1 g/day despite treatment with a maximally tolerated or allowed daily dose of RAS blockade (ACEi/ARB) for ≥ 3 months. Guideline recommendations indicate proteinuria reduction to under 1 g/day as a surrogate marker of improved kidney outcomes in IgAN. Furthermore, a reduction to under 1 g/day is a reasonable treatment target.

IX. Incremental levels of sustained proteinuria above 1 g/d are associated with marked changes in the risk of loss of kidney function. Reduction of proteinuria, ideally to under 1 g/d, is associated with favorable outcomes. The urinary protein-creatinine ratio (UPCR) has relatively poor correlation with 24-hour urine protein excretion, particularly when proteinuria is over 1 g/d. This makes distinguishing smaller changes in proteinuria (e.g., 1.5 vs 2 g/d) challenging. UPCR cannot be directly compared with a 24-h proteinuria level; however, UPCR gives the ability to overcome possible collection errors and deviations from normal creatinine excretion (e.g., physically active and muscular men). Due to this reason both can be used to assess proteinuria.

X. Budesonide (Tarpeyo) has not been included in KDIGO guidelines. Currently guidelines recommend enrollment into clinical trials prior to use of corticosteroids or other immunosuppressants. If the benefit outweighs the risk, treatment with prednisone or methylprednisolone is recommended based on limited clinical trial experience. Budesonide (Tarpeyo) was able to show sustained benefit UPCR reduction eGFR maintenance at two years. Other glucocorticoid therapies (prednisone, methylprednisolone, and IV methylprednisolone) have demonstrated similar reductions in proteinuria and have comparable safety profiles to budesonide (Tarpeyo). It is unknown if budesonide (Tarpeyo) is superior to other glucocorticoid

therapies that could be utilized. Additionally, budesonide (Tarpeyo) is significantly more costly than other glucocorticoid therapies. Of the other alternative agents, mycophenolate Mofetil (MMF) is the preferred option. There is limited clinical data to support the use of other immunosuppressive agents.

XI. Endpoints from other corticosteroid studies followed patients for up to 10 years. Safety and efficacy of treatment with subsequent courses of budesonide (Tarpeyo) have not been established at this time. Data to support possible retreatment with budesonide (Tarpeyo) is under evaluation in the NefigArd-OLE trial program. Similarly designed trials with long-term safety data have limited total glucocorticoid exposure to six months due to increased risks of treatment-related adverse events (infection risk, impaired glucose tolerance, weight gain, etc.).

Investigational or Not Medically Necessary Uses

I. Budesonide (Tarpeyo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. IgAN in members less than 18 years of age
      i. The use of budesonide (Tarpeyo) has not been evaluated in children. Additionally, while guidelines acknowledge use of immunosuppressants, specifically corticosteroids, are more widespread in children there is a lack of randomized controlled trials and consensus-driven indications for use in pediatric populations. As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.
   B. Secondary IgA Nephropathy
      i. Secondary IgAN can be attributed to a variety of other disorders including but not limited to cirrhosis and other severe forms of liver disease, celiac disease, HIV infection, monoclonal gammopathy of renal significance (MGRS), seronegative arthritis, etc. While there is no standard of care treatment for IgAN in these patients, therapy should be directed at the underlying primary disease.
   C. Budesonide (Tarpeyo) used in combination with Sparsentan (Filspari)
   D. Focal segmental glomerulosclerosis (FSGS)
   E. Chronic kidney disease (CKD) other than primary IgAN

References

1. Tarpeyo [Prescribing Information]. Stockholm, Sweden: Calliditas Therapeutics AB. December 2023.
2. Lafayette R, Kristensen J, Stone A, et al. Efficacy and safety of a targeted-release formulation of budesonide in patients with primary IgA nephropathy (NefIgArd): 2-year results from a randomised phase 3 trial [published correction appears in *Lancet*. 2023 Sep 9;402(10405):850]. Lancet. 2023;402(10405):859-870.
3. Fellström BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial. *Lancet*. 2017;389(10084):2117-2127. doi:10.1016/S0140-6736(17)30550-0
4. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100(4S):S1-S276. doi:10.1016/j.kint.2021.05.021

5. UpToDate, Inc. IgA nephropathy: Clinical features and diagnosis. UpToDate [database online]. Waltham, MA. Last updated February 9, 2022. Available at: http://www.uptodate.com/home/index.html.
6. UpToDate, Inc. IgA nephropathy: Treatment and prognosis. UpToDate [database online]. Waltham, MA. Last updated January 3, 2022. Available at: http://www.uptodate.com/home/index.html.
7. Pattrapornpisut, P., Avila-Casado, C., & Reich, H. N. (2021). Iga nephropathy: Core curriculum 2021. American Journal of Kidney Diseases, 78(3), 429–441. https://doi.org/10.1053/j.ajkd.2021.01.024

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
sparsentan (Filspari)	Primary IgA nephropathy; at high risk of progression

Policy Implementation/Update:

Action and Summary of Changes	Date
Added related policies table. Updated to allow a pathway to coverage through standard criteria.	01/2023
Policy created.	04/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP010

Split Fill Management* [Applies to Cabometyx ONLY]

Description

Cabozantinib (Cabometyx, Cometriq) is an orally administered tyrosine kinase inhibitor of RET, MET, VEGFR1/2/3, KIT, TRKB, FLT3, and TIE2.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*
cabozantinib (Cabometyx®)	20 mg tablet	Advanced and metastatic renal cell carcinoma (aRCC) Progressive or metastatic Hepatocellular (Liver) carcinoma (HCC), in patients previously treated with sorafenib Advanced or metastatic differentiated thyroid carcinoma (DTC) in patients previously treated with vascular endothelial growth factor (VEGF) targeted therapy	30 tablets/30 days
	40 mg tablet		30 tablets/30 days
	60 mg tablet		30 tablets/30 days
cabozantinib (Cometriq®)	60 mg per day blister cards	Progressive or metastatic medullary thyroid carcinoma	84 capsules/28 days
	100 mg per day blister cards		56 capsules/28 days
	140 mg per day blister cards		112 capsules/28 days

**Quantity limits are based on recommended daily dose of cabozantinib for each indication; QL exceptions allowed only for dose reductions*

Initial Criteria

I. **Cabozantinib (Cabometyx)** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by, or in consultation with, an oncologist; **AND**
   B. The member has a diagnosis of one of the following:
      1. **Differentiated Thyroid carcinoma (DTC); AND**
         i. Member is 12 years of age or older; **AND**
         ii. Disease is locally advanced or metastatic (stage III or IV); **AND**
         iii. Member has one of the following subtypes of DTC:
            a. Papillary thyroid carcinoma; **OR**
            b. Follicular thyroid carcinoma; **OR**
            c. Hürthle cell thyroid carcinoma; **AND**
         iv. The disease is refractory to radioactive iodine (RAI) treatment, or the member is not eligible for radioactive iodine treatment; **AND**
         v. Member has been previously treated with at least one vascular endothelial growth factor (VEGF) targeted therapy (e.g., Lenvatinib [Lenvima], sorafenib [Nexavar], etc.); **AND**
         vi. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
      2. **Renal cell carcinoma (RCC); AND**
         i. Member is 18 years of age or older; **AND**
         ii. Disease is advanced or metastatic (stage III or IV); **AND**
         iii. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
            a. Prescribed in combination with nivolumab (Opdivo); **OR**
      3. **Hepatocellular (Liver) carcinoma (HCC); AND**
         i. Member is 18 years of age or older; **AND**
         ii. Disease is progressive or advanced stage or greater (stage III or IV); **AND**
         iii. Member has been previously treated with a guideline-recommended first-line systemic therapy (e.g., atezolizumab with bevacizumab, tremelimumab-acti with durvalumab, sorafenib, Lenvatinib, durvalumab alone, pembrolizumab); **AND**
         iv. Provider attests the member has Child-Pugh class A liver function; **AND**
         v. Cabozantinib (Cabometyx) is prescribed as monotherapy

II. **Cabozantinib (Cometriq)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Treatment is prescribed by, or in consultation with, an oncologist; **AND**
   C. Member has a diagnosis of **medullary thyroid carcinoma (MTC)**; **AND**
      1. Disease is locally recurrent progressive or metastatic (stage III or IV); **AND**
      2. Cabozantinib (Cometriq) is prescribed as monotherapy; [cabozantinib (Cabometyx) should not be used for medullary thyroid carcinoma (MTC)].

III. Cabozantinib (Cabometyx or Cometriq) is considered investigational when used for all other conditions, including but not limited to:

A. Adrenocortical carcinoma
B. Anaplastic Thyroid Cancer
C. Breast cancer
D. Cervical Cancer
E. Cholangiocarcinoma
F. Colorectal cancer
G. Head and neck cancer
H. Merkel cell carcinoma and skin cancer
I. Multiple myeloma, acute myeloid leukemia
J. Neuroendocrine Tumors
K. Neurofibromas
L. Non-small cell lung cancer
M. Pheochromocytomas and paraganglioma
N. Prostate cancer
O. Salivary gland 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. Provider attests to or provides clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. A diagnosis of one the following:
    A. **Differentiated Thyroid Carcinoma (DTC)**; **AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
    B. **Renal Cell Carcinoma (RCC); AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
            ii. Cabozantinib (Cabometyx) is prescribed in combination with nivolumab (Opdivo); **OR**
    C. **Hepatocellular Carcinoma (HCC); AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
    D. **Medullary Thyroid Carcinoma (MTC)**; **AND**
            i. Cabozantinib (Cometriq) is prescribed as monotherapy

Supporting Evidence

I. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies such as multi-kinase inhibitors must be prescribed by, or in consultation with, an oncologist.
II. Cabozantinib (Cabometyx) carries three FDA approved indications and is used in the treatment of advanced renal cell carcinoma (RCC) with, or without, nivolumab (Opdivo), hepatocellular carcinoma (HCC) in patients previously treated with sorafenib, and advanced or metastatic differentiated thyroid carcinoma (DTC) patients previously treated with a vascular endothelial growth factor receptor (VEGFR) targeted therapy. Cabozantinib (Cabometyx) should only be

used for these indications due to its specific formulation, dosing, and packaging differences compared to Cabozantinib (Cometriq).

III. Efficacy and safety of cabozantinib (Cometriq) and cabozantinib (Cabometyx) has not been established in patients less than 18 years of age diagnosed with medullary thyroid carcinoma (MTC), RCC, and HCC. Only cabozantinib (Cabometyx) has been approved for ages 12 years and older in DTC.

IV. Multi-kinase inhibitors are considered medically necessary when used as monotherapy. Efficacy and safety have not been studied in combination with other oncology agents with the exception of cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) in the advanced RCC.

V. **Differentiated thyroid carcinoma (DTC)**

a. DTC is categorized into papillary, follicular, or Hürthle cell cancer subtypes and is unrelated to MTC due to differing pathophysiology, evaluation, and treatment strategies than MTC. Additionally, cabozantinib (Cabometyx) has not been studied for the treatment of MTC.

b. Cabozantinib (Cabometyx) is FDA approved in patients twelve years of age or older with locally advanced or metastatic DTC that are RAI-refractory or ineligible and have progressed on a prior VEGFR-targeted therapy (lenvatinib and/or sorafenib). Cabozantinib (Cabometyx) was evaluated for efficacy and safety in the treatment of DTC via a double-blind, placebo-controlled trial (COSMIC-311). Although the COSMIC-311 trial did not meet one of its co-primary endpoints of statistically significant objective response rate in the first 100 randomized patients versus placebo, the other co-primary endpoint, progression-free survival (PFS) in all patients, was met. Cabozantinib (Cabometyx) significantly reduced the risk of disease progression or death in the primary PFS analysis compared to placebo (median 11 months vs. 1.9 months [HR 0.22; 95% CI 0.15-0.31; p<0.0001]).

c. NCCN v3.2021 guidelines for thyroid carcinoma recommend lenvatinib as the first line preferred regimen in advanced or metastatic DTC. Cabozantinib (Cabometyx) received a Category 1 recommendation for patients that had progression on lenvatinib and/or sorafenib for advanced or metastatic DTC.

d. The recommended dose for cabozantinib (Cabometyx) is 60mg once daily for adults with BSA greater than, or equal to, 1.2 m^2 and 40 mg once daily in pediatric patients 12 years of age and older, with BSA less than 1.2m^2.

VI. **Renal Cell Carcinoma (RCC)**

a. The NCCN guidelines have been updated to favor the use of multi-TKI in combination with immune checkpoint inhibitors. Cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) joins lenvatinib in combination with pembrolizumab (Keytruda) as a first-line (category 1) treatment for clear-cell advanced RCC.

i. Cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) was studied against sunitinib in a phase 3, randomized, open-label trial (CheckMate-9ER, N=651). PFS was doubled with cabozantinib (Cabometyx) plus nivolumab than with sunitinib (median, 16.6 months vs. 8.3 months; HR 0.51; 95% CI, 0.41 to 064; P<0.0001). Additionally, overall survival (OS) was longer with cabozantinib (Cabometyx) in combination with nivolumab than with sunitinib (HR 0.60; 99% CI, 0.40 to 0.89; P = 0.001).

b. The NCCN guidelines recommend cabozantinib (Cabometyx) monotherapy as second-line (category 1) treatment in clear-cell advanced RCC and in first-line (category 2A) intermediate or poor-risk clear-cell advanced RCC.
    i. Cabozantinib (Cabometyx) was evaluated for the treatment of advanced RCC against everolimus in a phase 3 RCT (METEOR study). The open-label trial enrolled 658 patients with clear-cell advanced RCC that have trialed at least one prior anti-angiogenic therapy. Cabozantinib monotherapy showed a statistically significant improvement in progression-free survival, overall survival, and objective response rate compared to everolimus.
    ii. Additionally, cabozantinib (Cabometyx) monotherapy was evaluated for first line treatment for patients with intermediate or poor risk clear-cell advanced RCC against sunitinib in a phase 2, randomized, open-label trial (CABOSUN, N=157). Cabozantinib significantly prolonged PFS compared to sunitinib (median, 8.6 months vs. 5.3 months; HR 0.48; 95% CI, 0.31 to 074; P=0.0008).

VII. **Hepatocellular Carcinoma (HCC)**

a. Cabozantinib (Cabometyx) was evaluated in Child-Pugh class A patients with advanced and progressing hepatocellular carcinoma against a placebo. All patients had been previously treated with sorafenib in this phase III trial and had received a maximum of two previous systemic therapies for advanced hepatocellular carcinoma. Overall survival was statistically significantly longer with cabozantinib compared to placebo. (10.2 months vs. 8 months [HR 0.76; CI 0.63-0.92; p=0.005]).
b. NCCN guideline for HCC was recently updated to include atezolizumab (Tecentriq) and bevacizumab (Avastin) as the preferred first-line therapy (category 1 recommendation). Sorafenib (Nexavar) and lenvatinib (Lenvima) are other recommended monotherapy options for first-line therapy (category 1) in patients with a Child-Pugh Class A score [or class A/ B7 for sorafenib], and those who are treatment naïve in the first-line setting. Incidence of hematological, respiratory, and hepatic adverse reactions is significant with atezolizumab and bevacizumab regimen and in many situations, patients discontinue the regimen due to adverse reactions and transition to multi-TKI agents without having progressed on the first-line therapy. Cabozantinib monotherapy received a NCCN Category 1 recommendation along with regorafenib as subsequent-line therapy for patients with Child-Pugh A liver function following disease progression on or after sorafenib. Additionally, lenvatinib and sorafenib are also recommended as subsequent-line agents with category 2A NCCN recommendations should there be progression on first-line therapy with atezolizumab and bevacizumab. Other than sorafenib or nivolumab, there is no data to define optimal treatment for those who progress after first-line systemic therapy; therefore, treatment with cabozantinib (Cabometyx) for progressive HCC is recommended based on the clinical benefit limited to patients who progressed on sorafenib.

VIII. **Medullary thyroid carcinoma (MTC)**

a. MTC accounts for 1-2% of thyroid cancers in the United States and is characterized as sporadic or hereditary as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome with elevated calcitonin as a hallmark feature. MTC is not a type of DTC and cabozantinib (Cometriq) shall be used for MTC due to its specific formulary, dosing, and

packaging differences compared to cabozantinib (Cabometyx). Systemic treatment may be warranted in advanced and metastatic MTC for high volume, symptomatic, or progressive disease.

b. Cabozantinib (Cometriq) is FDA-approved for the treatment of medullary thyroid carcinoma in adult patients with progressive, metastatic disease in the phase III EXAM trial against a placebo. Patients in the trial had either hereditary, sporadic, or metastatic disease. Fifty nine percent of patients had a RET positive mutation while 40% had unknown RET mutation. Cabozantinib (Cometriq) demonstrated statistically significant median PFS compared to placebo (11.2 months vs. 4 months [HR: 0.28; 95% CI 0.19-0.40; p<0.001]). The follow up analysis, published in 2017, indicated that cabozantinib did not show a statistically significant difference in overall survival compared to placebo for the overall group of 330 patients; however, in an exploratory assessment of overall survival, cabozantinib showed a statistically significant difference in overall survival for the RET M918T mutation population (44.3 months vs 18.9 months [HR 0.60; CI 0.38-.094; p=0.03]). Cabozantinib and vandetanib received a category 1 preferred recommendation for advanced and metastatic medullary thyroid carcinoma in the NCCN v3.2021 guidelines, regardless of RET-mutation status. Additionally, cabozantinib (Cometriq) remains a preferred (category 1) systemic therapy for recurrent, persistent-locoregional or asymptomatic MTC, wherein genomic testing is not a recommended common practice. Selpercatinib and pralsetinib are FDA-approved in RET-mutated MTC and carry a category 2A recommendation for treatment.

Investigational or Not Medically Necessary Uses

I. Cabozantinib (Cabometyx or Cometriq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Adrenocortical carcinoma
   B. Anaplastic Thyroid Cancer
   C. Breast cancer
   D. Cervical Cancer
   E. Cholangiocarcinoma
   F. Colorectal cancer
   G. Head and neck cancer
   H. Merkel cell carcinoma and skin cancer
   I. Multiple myeloma, acute myeloid leukemia
   J. Neuroendocrine Tumors
   K. Neurofibromas
   L. Non-small cell lung cancer
   M. Pheochromocytomas and paraganglioma
   N. Prostate cancer
   O. Salivary gland 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. Cometriq [Package Insert]. South San Francisco, CA. Exelixis, Inc. January 2020.
2. Cabometyx [Package Insert]. Alameda, CA. Exelixis, Inc. September 2021.
3. Brose MS, Robinson B, Sherman SI, et al. Cabozantinib for radioiodine-refractory differentiated thyroid cancer (COSMIC-311): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2021;22(8):1126-1138.
4. Tuttle, MR. Differentiated thyroid cancer: Overview of management. Updated July 15, 2021. UpToDate, Post TW (Ed), *UpToDate*, Waltham, MA. Accessed March 6, 2022.
5. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841.
6. Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [protocol]. *N Engl J Med*. 2021;384(9):829-841
7. Choueiri TK, Hessel C, Halabi S, et al. Cabozantinib versus sunitinib as initial therapy for metastatic renal cell carcinoma of intermediate or poor risk (Alliance A031203 CABOSUN randomised trial): Progression-free survival by independent review and overall survival update. *European Journal of Cancer*. 2018;94:115-125.
8. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2016;17(7):917-927.
9. Abou-alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in Patients with Advanced and Progressing Hepatocellular Carcinoma. *N Engl J Med.* 2018;379(1):54-63.
10. Schoffski P., Elisei R., Muller S., et al. An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib in medullary thyroid carcinoma patients with document RECIST progression at baseline. *Journal of Clinical Oncology.* 30.(15). May 2012.
11. Elisei R, Schlumberger MJ, Müller SP, et al. Cabozantinib in progressive medullary thyroid cancer [published correction appears in J Clin Oncol. 2014 Jun 10;32(17):1864]. *J Clin Oncol*. 2013;31(29):3639-3646. doi:10.1200/JCO.2012.48.4659
12. Tuttle, MR. Medullary thyroid cancer: clinical manifestations, diagnosis, and staging. Updated July 13, 2020. *UpToDate*, Post TW (Ed), UpToDate, Waltham, MA. Accessed March 6, 2022.
13. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
14. National Comprehensive Cancer Network. Thyroid Carcinoma Version 3.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf. [Accessed February 22,2022].
15. National Comprehensive Cancer Network. Kidney Cancer Version 4.2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. [Accessed February 22, 2022].
16. National Comprehensive Cancer Network. Hepatobiliary Cancer Version 5.2021. Available at https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf. [Accessed February 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
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Thyroid Carcinoma
	Hepatocellular Carcinoma (HCC)
	Renal Cell Carcinoma (RCC)
	Soft Tissue Sarcoma (STS)
	Endometrial Carcinoma (EC)
selpercatinib (Retevmo™), 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
vandetanib (Caprelsa®)	Locally advanced or metastatic medullary thyroid cancer
everolimus (Afinitor®, Afinitor Disperz®)	Advanced Renal cell Carcinoma
	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
	Subependymal giant cell astrocytom
	Partial seizure, adjunct, tuberous sclerosis syndrome
	Subependymal giant cell astrocytoma
axitinib (Inlyta®)	Advance renal cell carcinoma
sunitinib (Sutent®)	Advance renal cell carcinoma
	Gastrointestinal stromal tumor
	Renal cell carcinoma, adjuvant following nephrectomy
	Neuroendocrine pancreatic tumor

Policy Implementation/Update

Action and Summary of Changes	Date
Updated hepatocellular carcinoma criteria to align with recent NCCN guidelines; Cabometyx may be used after any approved first line treatment.	05/2024
Updated policy to separate criteria for Cabometyx and Cometriq. Added criteria for Cabometyx in members 13 years of age and older in DTC. Added criteria for use of Cabometyx in combination with nivolumab in advanced RCC. Added Child-Pugh A liver function status requirement for Cabometyx in HCC given guidelines recommendations. Removed criteria requiring RET-mutation status for MTC. Removal of oncologist requirements upon renewal. Updated supporting evidence and references accordingly. Added anaplastic thyroid cancer, NETS, cervical cancer, NSCLC to E/I. Added Related Policies section.	03/2022
Transitioned criteria to policy format, added hepatocellular carcinoma indication, added age criteria and monotherapy criteria to all indications.	02/2019
Removed step therapy in RCC; Updated renewal language to assess response to therapy	01/2018
Previous Reviews	12/2012

calcifediol (Rayaldee®)

UMP POLICY

Policy Type: PA Pharmacy Coverage Policy: UMP088

Description

Calcifediol (Rayaldee) is an orally administered prohormone of vitamin D3, calcitriol (1,25-dihydroxyvitamin D3).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
calcifediol (Rayaldee)	30 mcg ER Capsule	Secondary hyperparathyroidism in Stage 3 or 4 CKD	60 capsules/30 days	195578

Initial Evaluation

I. Calcifediol (Rayaldee) may be considered medically necessary when the following criteria below are met:
   A. Member has a diagnosis of stage 3 (GFR 30-59 mL/min) or stage 4 (GFR 15-29 mL/min) chronic kidney disease (CKD); **AND**
   B. Member has a diagnosis of secondary hyperparathyroidism (enlarged parathyroid glands due to excessive secretion of parathyroid hormone) ; **AND**
   C. Member is **not** on dialysis; **AND**
   D. Member has a 25-hydroxyvitamin D serum level of < 30 ng/mL; **AND**
   E. Medication is prescribed by, or in consultation with a nephrologist or endocrinologist; **AND**
   F. Treatment with ALL the following has been ineffective, contraindicated, or not tolerated:
      i. calcitriol (Rocaltrol)
      ii. paricalcitol (Zemplar)

II. Calcifediol (Rayaldee) is considered investigational when used for all other conditions, including but not limited to:
   A. Chronic Kidney Disease (CKD) stages 1, 2 and 5 with hyperparathyroidism
   B. End Stage Renal Disease (ESRD) on dialysis with hyperparathyroidism
   C. Secondary hyperparathyroidism without CKD stage 3 or 4 diagnosis

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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. Medication is prescribed by, or in consultation with a nephrologist or endocrinologist; **AND**
IV. Member has a diagnosis of stage 3 (GFR 30-59 mL/min) or stage 4 (GFR 15-29 mL/min) chronic kidney disease (CKD); **AND**
V. Member has a diagnosis of secondary hyperparathyroidism (enlarged parathyroid glands due to excessive secretion of parathyroid hormone); **AND**
VI. Member is **not** on dialysis; **AND**
VII. Member has exhibited improvement or stability of disease symptoms defined by the following:
   A. Intact parathyroid hormone (PTH) remains above the treatment goal; **AND**
   B. Total 25-hydroxyvitamin D serum level is between < 100 ng/mL; **AND**
   C. Serum calcium < 9.8 mg/dL; **AND**
   D. Serum phosphorous < 5.5 mg/dL

Supporting Evidence

I. Calcifediol (Rayaldee) was studied in two identical multicenter, randomized, placebo-controlled, double-blind trials in 429 patients with secondary hyperparathyroidism with stage 3 or 4 CKD and serum concentration of 25-hydroxyvitamin D levels between 10 and 30 ng/mL.
II. The primary efficacy outcome was the reduction in plasma PTH from baseline when comparing calcifediol (Rayaldee) to placebo which were 33% versus 8% in trial one and 34% versus 7% in trial two by 26 weeks.
III. There is currently insufficient evidence to suggest that there is a difference between calcifediol ER (Rayaldee) from other vitamin D analogs.
IV. The treatment goal for intact PTH is patient dependent, and will be defined by the provider. In clinical trials the patient's Rayaldee dose was increased to 60 mcg per day when the intact PTH level was greater than 70 pg/mL, the serum 25-hydroxyvitamin D level was less than 65 ng/mL, and the serum calcium level was less than 9.8 mg/dL.
V. Stages of CKD

Stage	GFR (mL/min/1.73 m^2	
1	≥ 90	Normal kidney or high
2	60-89	Mildly reduced kidney function
3 A	45-59	Mild to moderately reduced kidney function
3 B	30-44	Moderate to severely reduced kidney function
4	15-29	Severely reduced kidney function
5	<15 or on dialysis	End stage kidney failure (sometimes called established renal failure)
Stage 1 or Stage 2 are not considered CKD in the absence of kidney damage		

Investigational or Not Medically Necessary Uses

I. There is currently limited evidence to suggest safety and/or efficacy with calcifediol (Rayaldee), when used for the treatment of CKD stage 1, 2, and 5, ESRD on dialysis, and secondary hyperarathyoroidism without CKD stage 3 or 4.

References

1. Rayaldee [Prescribing Information]. OPKO Pharmaceuticals, LLC. Miami, FL. March 2016.

Policy Implementation/Update:

Date Created	January 2017
Date Effective	February 2017
Last Updated	October 2019
Last Reviewed	01/2017, 02/2017, 10/2019

Action and Summary of Changes	**Date**
Criteria was transitioned into policy format with the addition of renewal criteria, investigational section, and supporting evidence.	10/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP025

Description

Erenumab (Aimovig), galcanezumab (Emgality), and fremanezumab (Ajovy) are subcutaneous injections of monoclonal antibodies that bind to the calcitonin gene-related peptide (CGRP) receptor or ligand. Rimegepant (Nurtec ODT) and atogepant (Qulipta) are orally administered CGRP receptor antagonists.

Length of Authorization

- Initial:
  - **rimegepant (Nurtec ODT)**
    - at a quantity less than, or equal to, 8 tablets per 30 days (categorized as treatment of acute migraine): 12 months
    - at a quantity of 9-16 tablets per 30 days (categorized as migraine preventive treatment, or preventive treatment should be considered prior to use of this quantity): Six months
  - **All other agents**
    - Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
erenumab (Aimovig)	Migraine prophylaxis	70 mg/1 mL autoinjector	1 mL/30 days
		140 mg/1 mL autoinjector	
galcanezumab (Emgality)	Migraine prophylaxis	120 mg/1 mL autoinjector	**Initial:** 2 mL (240 mg)/30 days for one fill **Maintenance:** 1 mL (120mg)/30 days
		120 mg/1 mL prefilled syringe	
	Episodic cluster headache	100 mg/1 mL prefilled syringe	3 mL/30 days
fremanezumab (Ajovy)	Migraine prophylaxis in adult and pediatric patients	225 mg/1.5 mL prefilled syringe	1.5 mL/30 days **OR** 4.5 mL per 90-day supply
		225 mg/1.5 mL autoinjector	
rimegepant (Nurtec ODT)	Acute migraine treatment Migraine prophylaxis	75 mg orally disintegrating tablet	8 tablets/30 days
			16 tablets/30 days
atogepant (Qulipta)	Migraine prophylaxis	10 mg tablet	30 tablets/30 days
		30 mg tablet	
		60 mg tablet	

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Initial Evaluation

Migraine

I. **Erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), and atogepant (Qulipta)** may be considered medically necessary when the following criteria are met:
   A. A diagnosis of migraine; **AND**
   B. Medications in this policy will not be used in combination with each other (exception: rimegepant (Nurtec ODT) at a dose of less than or equal to 8 tablets per 30 days); **AND**
   C. Medication overuse headache has been ruled out as the cause of, or as an aggravating contributor to, the member's migraines or cluster headaches; **AND**
   D. The member has a history of four or more monthly migraine days; **AND**
   E. The member has experienced migraine for one year or longer; **AND**
   F. The member has tried and failed, or is intolerant to, prophylactic therapy with at least one agent from two distinct groups listed below: (Note, if a class of agents is contraindicated, a trial and failure of at least two agents from the remaining groups is required.):
      1. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
      2. Group 2: amitriptyline, venlafaxine
      3. Group 3: topiramate, sodium valproate, divalproex sodium
      4. Group 4: candesartan; **AND**
   G. The patient has tried each of the prophylactic therapies at therapeutic doses for at least three months **OR** the member is intolerant of the therapies; **AND**
   H. The request is for **fremanezumab (Ajovy); AND**
      1. The member is 6 years or older; **AND**
      2. If between the age of 6 – 17 years: The member weights 45kg or more; **OR**
   I. The request is for **erenumab (Aimovig)** or **galcanezumab (Emgality); AND**
      1. The member is 18 years or older; **OR**
   J. The request is for **atogepant (Qulipta); AND**
      1. The member is 18 years or older; **AND**
      2. Treatment with fremanezumab (Ajovy), erenumab (Aimovig), and galcanezumab (Emgality) has been ineffective, contraindicated, or not tolerated

II. **Rimegepant (Nurtec ODT)** may be considered medically necessary when the following criteria below are met:
   A. The request is for less than, or equal to, 8 tablets per 30 days (categorized as treatment of acute migraine); **AND**
      1. Member is 18 years of age or older; **AND**
      2. Two oral, followed by one nasal*, and one injectable* serotonin 5-HT1 receptor agonists (i.e., sumatriptan, naratriptan, rizatriptan) have been ineffective, contraindicated, or not tolerated. (Please note: medications notated with an asterisk may require step therapy or non-formulary requirements prior to approval); **AND**
      3. Treatment with ubrogepant (Ubrelvy)* has been ineffective, contraindicated, or not tolerated; **OR**
   B. The request is for 9-16 tablets per 30 days (categorized as migraine preventive treatment, or preventive treatment should be considered prior to use of this quantity); **AND**
      1. Criteria I(A)-I(G) above are met; **AND**
      2. Member is 18 years of age or older; **AND**

3. Treatment with fremanezumab (Ajovy), erenumab (Aimovig), and galcanezumab (Emgality) has been ineffective, contraindicated, or not tolerated

Cluster Headache Prophylaxis

III. **Galcanezumab (Emgality)** may be considered medically necessary when the following criteria are met:
   A. Diagnosis of cluster headache; **AND**
   B. The provider attests the diagnosis is confirmed using the International Classification of Headache Disorders (ICHD) criteria for cluster headache; **AND**
   C. The member has had an adequate prophylactic therapy trial and failure (considered to be one month or longer), contraindication, or intolerance to verapamil **and** lithium concurrently or consecutively. (Note, if one is contraindicated, a trial of the other is required.)

IV. Erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), rimegepant (Nurtec ODT), and atogepant (Qulipta) are considered investigational when used for all other conditions, including but not limited to:
   A. Chronic cluster headache
   B. Episodic cluster headache, with the exception of galcanezumab (Emgality)
   C. Post-traumatic headache
   D. Pediatric headache or migraine, with the exception of fremanezumab (Ajovy)
   E. Vasomotor symptoms or hot flashes
   F. Fibromyalgia

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. **Diagnosis of migraine**; **AND**
      1. Request is for erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy); **AND**
         i. The medications in this policy will not be used in combination with each other; **AND**
         ii. The member has experienced a response to therapy, defined by a reduction of at least two migraine days per month compared to baseline upon first renewal; **OR**
            a. Upon subsequent renewals the member has maintained the initial response or gained further response to therapy; **OR**
      2. Request is for atogepant (Qulipta) or for 9-16 tablets per 30 days of rimegepant (Nurtec ODT); **AND**

i. Treatment with fremanezumab (Ajovy), erenumab (Aimovig), **and** galcanezumab (Emgality) has been ineffective, contraindicated, or not tolerated; **AND**
ii. The medications in this policy will not be used in combination with each other; **AND**
iii. The member has experienced a response to therapy, defined by a reduction of at least two migraine days per month compared to baseline upon first renewal; **OR**
a. Upon subsequent renewals the member has maintained the initial response or gained further response to therapy; **OR**

3. Request is for less than, or equal to, 8 tablets per 30 days of rimegepant (Nurtec ODT); **AND**
i. The member has experienced a response to therapy (e.g., reduction in symptoms, severity, or duration of migraine).

B. **Diagnosis of episodic cluster headache**; **AND**
1. The request is for galcanezumab (Emgality) only; **AND**
2. The member has experienced a response to therapy, defined by one of the following:
i. A reduction in four weekly cluster headache attacks compared to baseline; **OR**
ii. A complete reduction resolution of attacks (e.g., the member has a baseline of 3-4 attacks per week); **AND**
3. Provider attests the member continues to need therapy for cluster headache (i.e., the cluster period has not passed, or a trial of therapy taper has been attempted and was unsuccessful).

Supporting Evidence

I. There is a lack of safety and efficacy data in pediatrics; however, as of July 2019, clinical trials were underway for injectable CGRP agents in pediatrics.

II. There is lack of safety and efficacy data when CGRP agents are used concurrently. At acute dosing regimens, use of CGRP oral agents in combination with injectables for prophylaxis can be allowed given contraindications and tolerability challenges with triptans. Higher or frequent oral acute doses in combination with injectable CGRPs is not allowed. Combination use shall NOT be granted, nor should quantity exceptions. Historical studies of agents effecting CGRP have failed in clinical trials due to significant hepatotoxic safety concerns. The safety profile of increased CGRP inhibition is unknown with considerable safety risks at this time.

Acute Migraine Treatment:

III. After lifestyle modifications, non-pharmacologic therapies, and avoidance of triggers have been employed, pharmacologic therapy may be necessary. To which, triptans have an established safety and efficacy profile for the abortive treatment of migraine. Triptans are the mainstay of therapy and are recommended as first-line treatment by governing bodies and treatment guidelines such as American Academy of Neurology, American Family Physician, and American Headache Society. Triptans are not indicated for the continual prophylactic treatment of migraine.

Migraine Prophylaxis:

IV. In the pivotal trials for the agents listed in this policy, members had a history of four or more monthly migraine days for at least one year. Migraines may have numerous causes and triggers and may be transient in nature; thus, a strong history of migraine is warranted prior to consideration of coverage for CGRP agents.

V. Medication overuse headache (MOH) is a chronic daily headache or migraine secondary to acute medication in headache prone patients. In general, MOH presents in patients that use analgesics more than two to three days per week. Often, MOHs are refractory to both pharmacologic and non-pharmacologic therapies. The most effective way to treat MOH is to discontinue the overused medications, allow headaches to come back to baseline in number and severity, and then begin treatment with prophylactic therapy. Some of the agents in this policy have been shown to have efficacy in MOH, and others are under evaluation in clinical trials; however, the same considerations in III apply – the prescribing cascade should not continue with CGRP agents without first attempting to withdraw as many aggravating or unnecessary therapies if possible.

VI. The 2019 American Academy of Neurology (AAN) and American Headache Society (AHS) guidelines for adult migraine prophylaxis recommend select beta blockers, antidepressants, anticonvulsants, candesartan, and onabotulinum toxin A as efficacious or probably efficacious (Level A and B, respectively) for the prophylactic treatment of migraine in adults. If onabotulinum toxin A has been listed as a therapy that has been tried and failed this may be used as a qualifier of the two required agents to meet coverage consideration. Agents not listed specifically above in the policy have lower level, conflicting, or negative evidence. This includes, but is not limited to SSRIs, duloxetine, nortriptyline, cyproheptadine, clonidine, guanfacine, nebivolol, pindolol, carbamazepine, Lisinopril, calcium channel blockers, gabapentin, pregabalin, lamotrigine, oxcarbazepine, clomipramine, telmisartan, and benzodiazepines. Specifically, nortriptyline does not have the same level of efficacy supporting use for migraine prophylaxis as amitriptyline and should not be considered for adequate trials of prophylactic therapy.

- For pediatric migraine prevention, the 2019 AAN and AHS guidelines note that most children benefit from acute migraine treatment with behavioral and lifestyle changes for headache prevention and do not require additional pharmacologic or biobehavioral prevention. For those that additional migraine prevention should be considered when headaches occur with sufficient frequency and severity and result in migraine-related disability (undefined). The guidelines have not been updated to include recommendations for fremanezumab (Ajovy) in pediatrics. For pediatric patients requiring pharmacological treatment, guidelines recommend amitriptyline plus cognitive behavioral therapy (high confidence), topiramate (moderate confidence), propranolol (low confidence) (all level B recommendations), divalproex or derivatives (very low confidence), and onabotulinumtoxinA (very low confidence). The 2025 NICE guidelines recommend propranolol, topiramate, or amitriptyline for migraine prevention after a full discussion of benefits, risks, and suitability of each option. If the first treatment tried does not work, or is not tolerated, discuss trying a second option.
- Fremanezumab (Ajovy) received an age expansion to include pediatric patients 6 years and older who weigh 45kg or more with episodic migraines. FDA approval was based on the SPACE trial. The SPACE trial was a Phase III, multicenter, randomized, double-blinded, placebo-controlled trial that included participants 6 to 17 years old, weighing at least 45kg. Participants were required to have at episodic migraines (more than 4 but less than 15 monthly migraine days [MMD]) and those with history of hemiplegic migraines or nerve block were not permitted. The primary endpoint of mean change from baseline in the monthly average number of migraine days during

the 3-month treatment period was -2.5 in the fremanezumab (Ajovy) group vs -1.4 in the placebo group, difference of -1.0, P<0.021. The percentage of participants that had ≥50% MMD reduction was 47.2% vs 27% in the fremanezumab (Ajovy) group vs placebo, difference 20.2%, P<0.002. Reported adverse events include injection site reaction (15%), COVID19 (6%), nasopharyngitis (9%), URTI (5%), dizziness (6%), and headache (6%).

VII. A class review for migraine prophylactic therapies was completed in 2018, with conclusions that are consistent with guideline recommendations. The specific agents listed above, are shown to have the highest level of evidence for safety and efficacy.

VIII. Guidelines label a "treatment success" as a 50% reduction in migraine after three months of prophylactic therapy utilization. Additionally, some agents take one-to-three months to begin working. If the prophylactic therapies have not been trialed for three months, this does not constitute an adequate trial of that agent. Of note, adverse effects and contraindications may limit ability to utilize an agent, or class of agents, for three months and this should be taken into consideration when determining if criteria coverage has been met.

IX. In the absence of established differences in efficacy and/or safety amongst CGRP products, fremanezumab (Ajovy), erenumab (Aimovig), and galcanezumab (Emgality) have been chosen as the preferred products in this class. Treatment with, or contraindication to, these products is required prior to approval of others in the setting of chronic migraine.

Cluster Headache:

X. Cluster headaches are defined as severe, strictly unilateral pain, orbital, supraorbital, temporal or any combination of these, lasting 15-180 minutes and occurring from once every other day to eight times per day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness, or agitation. Cluster periods range from two weeks and three months

XI. Diagnostic criteria per ICHD3 include at least five attacks fulfilling the criteria in IX, either or both of the following: a sense of restlessness or agitation AND one of the following: conjunctival injections and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, miosis, and/or ptosis. Additionally, the diagnosis is not better accounted for by another IDHD3 diagnosis.

- Episodic is defined by the above occurring in periods lasting from seven days to one year, separated by pain free periods of at least three months.
- Chronic is defined as occurring for one year or longer without remission or with remission periods lasting less than three months

XII. Like migraine therapy, treatment for cluster headaches include acute/rescue therapy and prophylactic therapy; however, contrary to migraine, prophylactic therapy should be initiated without delay once a cluster headache bout begins.

- Acute therapies: Level A evidence includes: Supplemental oxygen, subcutaneous sumatriptan, and nasal zolmitriptan. Level B evidence includes: nasal sumatriptan, oral zolmitriptan, and sphenopalatine ganglion stimulation (not yet available in the U.S. outside of clinical trials). Therapies with convincing evidence for efficacy: octreotide, dihydroergotamine nasal spray, somatostatin, and corticosteroids.
- Prophylactic therapies: Level A evidence: suboccipital steroid injection as a transitional but not long term therapy. Several other therapies have been evaluated; however, available evidence coupled with expert opinion recommendations state verapamil and lithium should be first-line therapy; however, due to the 1-2 week onset of efficacy, transitional therapy is recommended with oral or subcutaneous steroids.

XIII. Galcanezumab (Emgality) was evaluated for safety and efficacy in episodic cluster headache. One Phase 3, RCT of 106 adult patients was conducted over eight weeks. This included those with episodic cluster headache in patients not on other therapies for headache prophylaxis. Patients were allowed to use acute/abortive headache treatment regimens (triptans, oxygen, APAP, NSAIDS). Patients with MOH were excluded. Outcomes included mean change from baseline in weekly cluster headache attach frequency from weeks one to three. Secondary endpoints included percentage of patients who achieved a response (50% or greater reduction from baseline in weekly cluster headache attack frequency) at week three, percentage of participants reporting a score of 1 or 2 on the PGI-I scale, and percentage of participants with suicidal behaviors assessed by C-SSRS.

XIV. Galcanezumab (Emgality) is indicated for the treatment of episodic cluster headache; however, a requirement of prophylactic therapy is required as prophylactic therapy should be administered without delay in all qualifying patients. Due to lack of long term safety and efficacy data, conventional therapy shall be tried prior to coverage consideration for galcanezumab (Emgality). Although the medication is not FDA approved for chronic cluster headache, there are very limited treatment options in this space beyond the conventional agents listed above. Additionally, there is an increased risk in suicidality in this population. If the medication is providing benefit to the member, as outlined in the criteria, and the clinical paradigm shifts from episodic to chronic cluster - benefits and risks of discontinuation or disapproved payment of the medication should be weighed.

Investigational or Not Medically Necessary Uses

I. The agents listed in this policy are being investigated for safety and efficacy in some the following indications. Safety and efficacy have not yet been established in all of the following:
   A. Chronic cluster headache
   B. Episodic cluster headache, with the exception of galcanezumab (Emgality)
   C. Post-traumatic headache
   D. Pediatric headache or migraine, with the exception of fremanezumab (Ajovy)
   E. Vasomotor symptoms or hot flashes
   F. Fibromyalgia

References

1. Emgality [Prescribing Information]. Eli Lilly and Company: Indianapolis, IN. June 2018.
2. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache. 2016;56(7):1093-106.
3. International Headache Society. Third edition of the International Classification of Headache Disorder (ICHD-3). Available at: https://ichd-3.org/. Published 2018. Accessed on July 3, 2019.
4. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. Cephalalgia. 2018;38(8):1442-1454.
5. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. JAMA Neurol. 2018;75(9):1080-1088.
6. Novartis. A study evaluating the effectiveness of AMG 334 injection in preventing migraine in adults having failed other therapies (LIBERTY). Available from: https://clinicaltrials.gov/ct2/show/NCT03096834. NLM identifier: NCT03096834. Accessed June 26, 2018.
7. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia. 2018;38(6):1026-1037.

8. Goadsby PJ, Reuter U, Hallström Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. N Engl J Med. 2017;377(22):2123-2132.
9. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomized, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017;16(6):425-434.
10. Ajovy (fremanezumab-vfrm) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA Inc; August 2025.
11. S ilberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. N Engl J Med. 2017;377(22):2113-2122.
12. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. JAMA. 2018;319(19):1999-2008.
13. Botox [Prescribing Information]. Allergan Inc. Irvine, CA. May, 2018.
14. Aimovig [Prescribing Information]. Amgen Inc. and Novartis Pharmaceuticals Corporation: Thousand Oaks, CA and East Hanover, NJ. May, 2018.
15. Durham PL. Calcitonin gene-related peptide (CGRP) and migraine. Headache. 2006;46 Suppl 1:S3-8.
16. Gilmore B, Michael M. Treatment of acute migraine headache. Am Fam Physician. 2011;83(3):271-80.
17. Weatherall MW. The diagnosis and treatment of chronic migraine. Ther Adv Chronic Dis. 2015;6(3):115-23.
18. Nurtec ODT [Prescribing Information]. Biohaven Pharmaceuticals. New Haven, CT. March 2020.
19. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet. 2021;397(10268):51-60.
20. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015;55(1):3-20.
21. Gilmore G., Geffen D., Michael M., et al. Treatment of acute migraine headaches. Am Fam Physician. 2011;83(3):271-280.
22. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache: The Journal of Head and Face Pain*. Published online December 10, 2018:head.13456.
23. Goadsby PJ, Dodick DW, Ailani J, et al. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. Lancet Neurol. 2020;19(9):727-737.
24. Ailani J, Lipton RB, Goadsby J, et al. Atogepant significantly reduces mean monthly migraine days in the phase 3 trial (ADVANCE) for the prevention of migraine. Migraine Trust Virtual Symposium; October 3-9, 2020. (additionally; data on file from Allergan/Abbvie).
25. Qulipta [Prescribing Information]. Allergan Pharmaceuticals International Limited, an AbbVie company: Dublin, Ireland. September 2021.
26. Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019;93(11):500-509.
27. Headaches in over 12s: diagnosis and management. London: National Institute for Health and Care Excellence (NICE); 2025 Jun 3. (NICE Clinical Guidelines, No. 150.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK553317/
28. A Study to Test if Fremanezumab is Effective in Preventing Episodic Migraine in Patients 6 to 17 Years of Age. Clinical Trial Registry identifier: NCT04458857. June 22, 2025.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to include Ajovy age expansion to 6 years and older (and at least 45kg)	10/2025
Added Aimovig and Emgality to preferred status and updated to trial of two generic preventive therapies. Added candesartan to generic preventive options per guideline update. Added trial of Ubrelvy to Nurtec criteria.	07/2024
Removed restriction of combination use with onabotulinum toxin (Botox) based on real world evidence suggesting additive benefit for chronic migraines with no significant safety signals identified.	10/2023
Updated initial approval duration to 6 months for all products and to one year for acute treatment setting.	04/2022
Removed trial of triptan agents upon renewal of Nurtec. Restructured Nurtec requirements to improve clarity.	02/2022
Added migraine requirement in Nurtec; Restructured Nurtec requirements breaking down based on treatment setting (acute tx vs phx) in both initial and renewal; Removed age requirement upon renewal.	10/2021
Addition of new product atogepant (Qulipta) into policy, aligning non-preferred CGRP agents	09/2021

Addition of Nurtec ODT into policy (initial and renewal): reviewing coverage/setting of Nurtec via quantity requested; in migraine prophylaxis section aligned Nurtec ODT with non-preferred CGRP agents. Addition of standard language to renewal criteria addressing use of samples. Updates to supporting evidence.	04/2021
Update to require treatment of Ajovy prior to Aimovig or Emgality in the setting of migraines	01/2021
Added Ajovy autoinjector to policy	04/2020
Removed PFS and 2-pack of Aimovig from policy as it is no longer available one the market	02/2020
Rearranged formatting for consistency between lines of business	11/2019
Criteria update: Transition from criteria to policy and compilation of all injectable CGRP therapies into one policy. Updated Aimovig quantity limit to 30 days vs 28 to align with other agents. Added comment that these therapies will not be used in combination with one another, clarified prophylactic requirement for migraine indication, reworded renewal criteria. Added Emgality new indication of cluster headache.	07/2019
No changes made	01/2019
Criteria update: Changed onabotulinum toxin requirement to three months versus previous four months of washout. Updated renewal questions to specify a reduction in monthly migraine days by two.	10/2018
Criteria created	10/2018

cannabidiol (Epidiolex®)

UMP POLICY

Policy Type: PA Pharmacy Coverage Policy: UMP011

Description

Cannabidiol (Epidiolex) is an orally administered cannabinoid.

Length of Authorization

- Initial: Twelve months
- Renewal: Twelve months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cannabidiol (Epidiolex)	100 mg/mL oral solution/kit	Lennox-Gastaut Syndrome Dravet Syndrome	20 mg/kg/day (round up to nearest pack size)
		Tuberous Sclerosis Complex	25 mg/kg/day (round up to nearest pack size)
	60 mg/mL oral solution/kit	Lennox-Gastaut Syndrome Dravet Syndrome	20 mg/kg/day (round up to nearest pack size)
		Tuberous Sclerosis Complex	25 mg/kg/day (round up to nearest pack size)

Initial Evaluation

I. Cannabidiol (Epidiolex) may be considered medically necessary when the following criteria below are met:
   A. Member is one year of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of the member's weight that has been measured in the past three months; **AND**
   D. Cannabidiol (Epidiolex) will be used in combination with one or more anticonvulsant medications; **AND**
   E. A diagnosis of one of the following:
      1. **Lennox-Gastaut Syndrome**; **OR**
      2. **Tuberous Sclerosis Complex**; **OR**
      3. **Dravet Syndrome**; **AND**
         i. Cannabidiol (Epidiolex) will **not** be used in combination with fenfluramine (Fintepla); **AND**
   F. Member's seizures are refractory to two or more anticonvulsant medications (e.g., clobazam [Onfi], valproate [Depakote], lamotrigine [Lamictal], levetiracetam [Keppra], rufinamide [Banzel], topiramate [Topamax], felbamate [Felbatol], stiripentol [Diacomit], zonisamide [Zonergan], vigabatrin [Sabril])

II. Cannabidiol (Epidiolex) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
   A. Infantile Spasms
   B. Other non-FDA approve seizure disorder
   C. Substance use disorder
   D. Prader-Willi Syndrome
   E. Gastrointestinal disorders
   F. Parkinson's Disease/Essential tremors

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. A diagnosis of one of the following:
   A. **Lennox-Gastaut Syndrome**; **OR**
   B. **Tuberous Sclerosis Complex**; **OR**
   C. **Dravet Syndrome**; **AND**
      1. Cannabidiol (Epidiolex) will not be used in combination with fenfluramine (Fintepla); **AND**
IV. Documentation of the member's weight that has been measured in the past three months; **AND**
V. Cannabidiol (Epidiolex) will continue to be used in combination with at least one other anti-epileptic medication (i.e. used as adjunct therapy) such as clobazam, valproate, levetiracetam, rufinamide, topiramate, felbamate, stiripentol, zonisamide, vigabatrin or lamotrigine; **AND**
VI. Documentation that the member has exhibited improvement or stability of disease symptoms [e.g., reduction in seizure frequency].

Supporting Evidence

I. Cannabidiol (Epidiolex) (CBD) is indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS), Dravet syndrome (DS), or Tuberous Sclerosis Complex (TSC) in patients one year of age and older. It received initial approval for treatment of seizures associated with LGS and DS for patients two years of age and older. This approval was expanded in 2020 to include new indication of seizures associated with TSC in patients one year and older. Additionally, CBD also received approval for expanded age range (one year and older) for patients with LGS and DS.
II. Differential diagnosis of LGS, DS, or TSC require detailed clinical examination in combination with advanced testing such as MRI, EEG, and genetic screening (SCN1A mutation for DS). Given the complexities of diagnosing and treating these conditions, supervision of treatment by a neurologist is required.

III. CBD was studied in four Phase 3, double blind, randomized placebo-controlled clinical trials in patients with baseline characteristics of history of use of two or more antiepileptic drugs (AED). Efficacy of CBD for LGS was studied in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years old. Study 1 (N=171) compared a dose of Epidiolex 20 mg/kg/day with placebo, while Study 2 (N=225) used 10 mg/kg/day and 20 mg/kg/day doses with a match with placebo. In both studies, patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. At 14 weeks, the median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for both dosage groups of CBD versus placebo with an observed reduction in drop seizures frequency within 4 weeks of initiating treatment.

IV. Study 3 (N= 120) assessed efficacy and safety of CBD for the treatment of convulsive seizures (tonic, clonic, atonic, and tonic-clonic) associated with DS in patients refractory to at least 2 AEDs. The median percent change from baseline (reduction) in the frequency of convulsive seizures was significantly greater for CBD 20 mg/kg/day treatment arm as compared to placebo (-39% versus -13%; *p*= 0.01).

V. Participants in study 4 (N=224) were aged 1 to 65 years. Cannabidiol (Epidiolex) was evaluated at 25 mg/kg/day (CBD25) and 50 mg/kg/day (CBD50) doses with a matching placebo, for efficacy in treatment of seizures (focal, tonic, clonic, atonic or tonic-clonic) associated with TSC. At 16 weeks cut-off, Percent reduction (per 28 days) in TSC-associated seizure frequency was significantly higher for CBD25 cohort (48.6%) and CBD50 cohort (47.5%) vs placebo (27%; p=0.0009 and p=0.0018, respectively). Ninety-nine percent (N=199) of the patients from the initial 16-week controlled trial elected to continue into a 48-week open-label extension phase, wherein safety of CBD was assessed. Although most common adverse reactions (diarrhea, anorexia and somnolence) were mild to moderate the CBD50 cohort reported higher incidence of AE including liver function impairment (ALT and/or AST elevation).

VI. CBD can cause dose-related elevations of liver transaminases (ALT and/or AST). In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages) and TSC (25 mg/kg/day), the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 13% (10 and 20 mg/kg/day dosages) and 12% (25 mg/kg/day dosage) in CBD-treated patients compared with 1% in patients on placebo. Assessment of liver function (ALT, AST, total bilirubin) is recommended prior to initiating treatment with CBD, with dose changes, or with the addition of, or changes in, hepatotoxic medications.

VII. During clinical trials for all FDA-approved indications, participants received CBD as an adjunct therapy. Majority of participants in these trials were receiving a median of 2 concomitant antiepileptic drugs (AED). Inclusion in clinical trial also required documentation of seizures above the minimum threshold (≥ 8 drop seizures per 28 days for LGS, ≥ 4 convulsive seizures per 28 days for DS, and ≥ 8 seizures per 28 days for TSC). Efficacy and safety of CBD as monotherapy has not been studied and remains unknown.

Investigational or Not Medically Necessary Uses

I. There are ongoing trials for infantile spasms, substance use disorder, Prader-Willi Syndrome, gastrointestinal disorders, Parkinson's disease/essential tremors, and other seizure disorders, therefore these indications are considered investigational at this time.

References

1. Epidiolex [Prescribing Information]. Greenwich Biosciences: Carlsbad, CA; July 2020.
2. Arzimanoglou A, French J, Blume WT et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *Lancet Neurol*. 2009 Jan;8(1):82-93. PMID: 19081517.
3. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav*. 2017 May;70(Pt B):313-318. E-published ahead of print 2017 Jan 10. PMID: 28087250.
4. Kanner AM, Ashman E, Gloss D et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy. *Neurology*. 2018; 0: 1-9. E-published ahead of print 2018 Jun 13. PMID: 29898974.
5. UpToDate, Inc. Dravet syndrome: Management and prognosis. *UpToDate* [database online]. Last updated September 2017.
6. UpToDate, Inc. Epilepsy syndromes in children. *UpToDate* [database online]. Last updated July 2018.
7. Wirrell EC, Laux L, Donner E et al. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations from a North American Consensus Panel. *Ped Neurol*. 2017 Mar; 68:18-34. e3. E published ahead of print 2017 Feb 4. PMID: 28284397.
8. Sahebkar F, Thiele E, Bebin EM, Bhathal H et al.; Cannabidiol (CBD) treatment in patients with seizures associated with tuberous sclerosis complex (TSC): a randomized, double-blind, placebo-controlled phase 3 trial (GWPCARE6), 2020, Developmental Medicine and Child Neurology; 62,13; conference abstract.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added in Epidiolex 60mg/mL product	10/2020
Updated policy to include new indication for cannabidiol (Epidiolex) for treatment of seizures associated with Tuberous Sclerosis Complex (TSC); updated policy format for consistency of requirements for coverage for each approved indication; added weight-based dosing and quantity limit; renewal criteria and supporting evidence section were updated	10/2020
Policy created	01/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP301

Split Fill Management*

Description

Capivasertib (Truqap) is an orally administered kinase inhibitor selective for all three isoforms of AKT (*AKT1, AKT2, AKT3*).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
capivasertib (Truqap)	Breast cancer, HER2-negative, HR-positive, *PIK3CA/AKT1/PTEN*-mutated, advanced, or metastatic	160 mg tablets	64 tablets/28 days
		200 mg tablets	
		160mg Therapy Pack	
		200mg Therapy Pack	

Initial Evaluation

I. **Capivasertib (Truqap)** 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. Medication will be used in combination with fulvestrant (Faslodex); **AND**
   D. Medication will not be used in combination with any other oncology therapy except for fulvestrant (Faslodex); **AND**
   E. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. The breast cancer is HR-positive, and HER2-negative; **AND**
      2. Documentation of at least one phosphatidylinositol 3-kinase (*PIK3CA*), serine/threonine protein kinase (*AKT1*), or phosphatase and tensin homolog (*PTEN*)-mutation; **AND**
         i. The member has had disease progression on at least one prior endocrine therapy for advanced or metastatic breast cancer (e.g., letrozole, anastrozole, exemestane, tamoxifen), unless not tolerated or contraindicated; **AND**
         ii. The member has had disease progression on, or after, treatment with a CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.), unless not tolerated or contraindicated; **OR**

3. The member has had disease recurrence on or within 12 months of completing endocrine-based (neo)adjuvant therapy (e.g., tamoxifen, anastrozole, exemestane, letrozole), unless not tolerated or contraindicated

II. Capivasertib (Truqap) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Second line treatment and beyond in non-altered *PIK3CA/AKT/PTEN*, HR+, HER2-, advanced or metastatic breast cancer

III. Capivasertib (Truqap) is considered investigational when used for all other conditions, including but not limited to:
   A. Capivasertib (Truqap) used in combination with oncology therapy other than fulvestrant (Faslodex)
   B. Capivasertib (Truqap) used to treat cancers other than breast cancer
   C. Triple negative breast 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. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Capivasertib (Truqap) is indicated in combination with fulvestrant for the treatment of adult patients with hormone-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), locally advanced, or metastatic breast cancer with one or more *PIK3CA/AKT1/PTEN*-alterations following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.
II. Capivasertib (Truqap) is not FDA approved and has not been studied in patients under 18 years of age. Safety and efficacy in the pediatric/adolescent population remains undetermined.
III. Given the complexities involved with the diagnosis, treatment approaches, and management of therapy for the indicated population, treatment with capivasertib (Truqap) should be initiated by or in consultation with an oncologist.
IV. Capivasertib (Truqap) is not FDA approved and has not been well studied in combination with oncolytic therapies other than fulvestrant at this time. Safety and efficacy of monotherapy with capivasertib (Truqap) or in combination with regimens other than fulvestrant remains undetermined.
V. Capivasertib (Truqap) was studied in combination with fulvestrant in Phase 2 (FAKTION) and Phase 3 (CAPItello-291) 1:1 randomized, double-blind, placebo-controlled trials in 848 patients with advanced or metastatic HR+, HER2- breast cancer. The Phase 3 trial included about 70% of patients refractory to CDK 4/6 inhibitors while the Phase 2 trial included patients refractory to

aromatase inhibitors only. Trial participants were mostly postmenopausal females aged 60 years old with a median of one previous line of therapy for advanced disease. Around 40-45% of patients in both trials had PIK3CA/AKT/PTEN pathway alterations. The primary efficacy outcomes were progression-free survival (PFS) and secondary outcomes included overall survival (OS) and health-related quality of life (HRQoL). In the Phase 3 trial, the primary endpoint, PFS, was statistically significant in favor of capivasertib (Truqap) at 7.3 months vs 3.1 months and OS was not yet reached in the PIK3CA/AKT/PTEN altered population only. In the Phase 2 trial, PFS was 12.8 months vs 4.6 months and median OS was 38.9 months vs 20.0 months in favor of capivasertib (Truqap) in the PIK3CA/AKT/PTEN altered population. HRQoL did not improve or deteriorate significantly in the capivasertib (Truqap) arm, except for worsening diarrhea. The overall confidence in that the therapy brings significant value is low at this time due to unknown impact on overall survival, lack of HRQoL benefit, lack of long-term safety data, and significant safety concerns associated with PI3K inhibitors.

VI. Documentation of one of the following mutations/alterations is required when considering an appropriate patient candidate for treatment with capivasertib (Truqap): *PIK3CA, AKT, or PTEN*. The Phase 3 CAPItello-291 clinical trial demonstrated that capivasertib (Truqap) is active in patients with the aforementioned mutations only. A subgroup analysis of the non-altered cohort did not demonstrate statistically significant differences against placebo.

VII. The CAPItello-291 Phase 3 clinical trial established the place in therapy and population likely to benefit from treatment with capivasertib (Truqap). As such, the place in therapy is as second-line treatment in the recurrent unresectable (advanced) or metastatic breast cancer setting. Treatment with National Comprehensive Cancer Network (NCCN) breast cancer guideline first-line recommended therapies is required prior to capivasertib (Truqap) which includes CKD 4/6 inhibitors in combination with aromatase inhibitors (AI) or fulvestrant. Those with disease recurrence on or within 12 months of completing endocrine-based adjuvant therapy (e.g., tamoxifen, anastrozole, exemestane, letrozole) are also considered appropriate candidates for therapy as this aligns with the inclusion criteria of the CAPItello-291 clinical trial.

Investigational or Not Medically Necessary Uses

I. Capivasertib (Truqap) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Second line treatment and beyond in non-altered *PIK3CA/AKT/PTEN*, HR+, HER2-, advanced or metastatic breast cancer
      i. CAPItello-291 Phase 3 clinical trial established that treatment with capivasertib (Truqap) in patients without the *PIK3CA, AKT,* or *PTEN* mutation did not achieve statistically significant difference in PFS against placebo. Due to lack of efficacy, use of capivasertib (Truqap) is considered not medically necessary in this population.
   B. Capivasertib (Truqap) used in combination with oncology therapy other than fulvestrant (Faslodex)
      i. Capivasertib (Truqap) is being studied in a Phase 3 trial (NCT04862663; CAPItello-292) in combination with a CDK4/6 inhibitor and fulvestrant in the first line setting for advanced/metastatic breast cancer. Study completion is estimated in 2029. Requests in the first line setting or in combination with a CDK4/6 inhibitor are considered experimental and investigational at this time.
   C. Capivasertib (Truqap) used to treat cancers other than breast cancer.

i. Capivasertib (Truqap) is being studied in a Phase 3 trial (NCT05348577; CAPItello 280) in combination with docetaxel in metastatic castration resistant prostate cancer. Study completion is estimated in 2026. Requests for this indication are considered experimental and investigational at this time.

D. Triple negative breast cancer
   i. Capivasertib (Truqap) is being studied in a Phase 3 trial (NCT03997123; CAPItello-290) in combination with paclitaxel as first-line treatment for patients with locally advanced or metastatic triple negative breast cancer. The study is estimated to be completed by 03/2024 with data read out in 2024-2025. Requests for this indication are considered experimental and investigational at this time.

** 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. Truqap. Package Insert. AstraZeneca Pharmaceuticals LP; November 2023.
2. National Comprehensive Cancer Network. Breast Cancer. NCCN. January 25, 2024. Accessed March 8, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
3. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2023;388(22):2058-2070. doi:10.1056/NEJMoa2214131
4. Howell SJ, Casbard A, Carucci M, et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive, HER2-negative breast cancer (FAKTION): overall survival, updated progression-free survival, and expanded biomarker analysis from a randomised, phase 2 trial. Lancet Oncol. 2022;23(7):851-864. doi:10.1016/S1470-2045(22)00284-4
5. Jones RH, Casbard A, Carucci M, et al. Fulvestrant plus capivasertib versus placebo after relapse or progression on an aromatase inhibitor in metastatic, oestrogen receptor-positive breast cancer (FAKTION): a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2020;21(3):345-357. doi:10.1016/S1470-2045(19)30817-4

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
alpelisib (Piqray, Vijoice)	Breast cancer, HR+, HER2-, PIK3CA+, advanced or metastatic
Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer, HER2-, HR+, advanced or metastatic
elacestrant (Orserdu)	Breast cancer, HR+, HER2-, ESR-1+, advanced or metastatic

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP012

Description

Caplacizumab-yhdp (Cablivi) is a von Willebrand factor (vWF) - directed antibody fragment (called a Nanobody) that inhibits the interaction between vWF and platelets, thereby reducing both vWF-mediated platelet adhesion and platelet consumption.

Length of Authorization

- Initial: 30 days
- Renewal: 28 days

Quantity limits

Dosage Form	Indication	Quantity Limit	DDID
Initial Request			
11mg vial	aTTP	30 vials/30 days	205773
Renewal Request			
11mg vial	aTTP	28 vials/28 days	205773

Initial Evaluation

I. Caplacizumab-yhdp (Cablivi) may be considered medically necessary when the following criteria below are met:
   A. Member is an adult age 18 and over; **AND**
   B. Prescribed in consultation with a hematologist; **AND**
   C. First administration will be done as an inpatient intravenous bolus infusion under the supervision of a healthcare professional; **AND**
   D. Caplacizumab (Cablivi) will be continued for 30 days beyond the last plasma exchange; **AND**
   E. A diagnosis of **acquired thrombotic thrombocytopenic purpura (aTTP)** when the following are met:
      1. Member has thrombocytopenia and microscopic evidence of red blood cell fragmentation (e.g. schistocytes); **AND**
      2. Taken in a regimen that includes both plasma exchange and an immunosuppressant (i.e. Rituximab, glucocorticoids); **AND**
      3. One of the following:
         i. A suppressed or deficient level of ADAMTS13*
         ii. A PLASMIC score to indicate an intermediate to high risk of ADAMTS13 deficiency, defined as a level less than or equal to 10% (5 to 7 points).
         iii. Presentation of severe features, including, but not limited to the following:
            a. Neurologic findings such as seizures, focal weakness, aphasia, dysarthria, confusion, coma
            b. Symptoms suggesting encephalopathy

c. High serum troponin levels

II. Caplacizumab (Cablivi) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Adjunct to treatments of thrombocytopenia other than plasma exchange and immunosuppressant.

III. Caplacizumab (Cablivi) is considered investigational when used for all other conditions, including but not limited to:
   A. Idiopathic thrombocytopenia
   B. Hereditary thrombotic thrombocytopenic purpura (TTP)
   C. Drug-induced thrombotic microangiopathy
   D. Hemolytic uremic syndrome
   E. Complement-mediated TMA
   F. Diarrheal hemolytic uremic syndrome
   G. Thrombocytopenia in pregnancy

Renewal Evaluation

I. Member has received caplacizumab (Cablivi) in combination with plasma exchange and immunosuppressive therapy for 30 days beyond the last plasma exchange; **AND**
II. Member has documented signs of persistent underlying disease with documentation of suppressed ADAMTS13 activity level; **AND**
III. Treatment will be extended one-time for a maximum of 28 days following the initially approved treatment course; **AND**
IV. Patient has not experienced more than 2 recurrences* while on caplacizumab (Cablivi).

Supporting Evidence

I. Caplacizumab (Cablivi) was studied and approved for the treatment of aTTP combination with plasma exchange and immunosuppressant in adult subjects age 18 years and older, under the supervision of a medical specialist.
II. Initial administration is performed as an inpatient, by intravenous bolus infusion, followed by subcutaneous injection. There is the potential for outpatient self-administration of subcutaneous injection, especially following the discontinuation of plasma exchange.
III. Diseases of thrombotic microangiopathy have varied etiologies and rule-out of differential diagnoses is important to determine effective and safe therapy. In practice, most hospitals do not have access to on-site testing for ADAMTS13 level. Results are typically delayed by use of off-site laboratories for confirmation as standard therapy is initiated.
   - An ADAMTS13 level is of less than ten percent would indicate a severe case;
   - Laboratory outcome may be pending at time of initial authorization request;
   - Laboratory outcome of ADAMTS13 is required upon renewal request.

IV. The PLASMIC scoring system is a validated diagnostic tool used to discriminate between the likelihood of ADAMSTS13 deficiency and other potential causes of microangiopathic hemolysis.
    - Scoring
        i. Low risk category
            1. Score of 0-4
            2. Indicates a risk of severe ADAMTS13 deficiency (levels less than or equal to 10%) in 4.3%.
        ii. Intermediate risk category
            1. Score of 5-6
            2. Indicates a 56.8% likelihood of severe ADAMTS13 deficiency involvement.
        iii. High risk category
            1. Score of 7
            2. Indicates a 96.2% likelihood of severe ADAMTS13 deficiency
    - Pre-existing liver or renal disease can falsely lower PLASMIC score.

V. Standard therapy of plasma exchange is initiated as soon as possible to mitigate the progressive course of neurologic deterioration, cardiac ischemia, irreversible renal failure and death.

VI. Treatment of initial acute episode with caplacizumab (Cablivi) is continued for at least 30 days following the last plasma exchange.

VII. *Terminology used in the setting of aTTP include the following:
    - Response: normalization or stabilization of platelet count with plasma exchange.
    - Remission: maintenance of normal platelet count for 30 days after stopping plasma exchange.
    - Relapse: recurrence of TTP following remission.
    - Exacerbation: recurrent thrombocytopenia within 30 days of stopping plasma exchange

VIII. The extension of treatment in the event of relapse may be considered when member experiences one of the following:
    - A return of the clinical signs and symptoms of aTTP;
    - Deficient ADAMTS13 level.

Investigational or Not Medically Necessary Uses

I. Include but are not limited to: Idiopathic thrombocytopenia, hereditary thrombotic thrombocytopenic purpura (TTP), drug-induced thrombotic microangiopathy, hemolytic uremic syndrome, complement-mediated TMA, thrombocytopenia in pregnancy
    A. Diseases of thrombotic microangiopathy have varied etiologies and effective therapies.
    B. Acquired thrombolic thrombocytopenia purpura is due to severely deficient levels of protease ADAMTS13, which manages thrombotic microangiopathy by limiting uncleaved vWF. Uncleaved vWF cause platelet consumption and thrombic microangiopathy by adhesion to platelets.
    C. Caplacizumab (Cablivi) prevents adhesion between vWF and platelets.

References

1. Cablivi [prescribing information]. Cambridge, MA: Genzyme Corporation; February 2019.

2. FDA approves first therapy for the treatment of adult patients with a rare blood clotting disorder. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630851.htm
3. UpToDate, Inc. Acquired TTP: Clinical manifestations and diagnosis. UpToDate [Online Database]. Waltham, MA. Last updated April 23, 2018. Available from: http://uptodate.com/home/index.html. Accessed February 12, 2019.
4. UpToDate, Inc. Acquired TTP: Initial treatment. UpToDate [Online Database]. Waltham, MA. Last updated February 7, 2019. Available from: http://uptodate.com/home/index.html. Accessed February 12, 2019.
5. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. NEJM; Jan 2019; 380(4): 335-46.
6. Duggan, S. Caplacizumab: First global approval. Drugs; Oct 2018; 78:1639-1642.
7. George, JN. Thrombotic thrombocytopenic purpura. NEJM; 2006; 354:1927-35.
8. Sadler, JE. Pathophysiology of thrombotic thrombocytopenic purpura. Blood; Sept 2017; 130(10): 1181-88..
9. Bendapudi PK, et al. Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study. Lancet Hematology 2017;4:e157-64
10. Williams LA, Marques MB, Pathology Consultation of the Diagnosis of Thrombotic Microangiopathies (TMAs), Am J Clin Pathol February 2016;145:158-165 DOI: 10.1093/AJCP/AQV086

Policy Implementation/Update:

Date Created	March 2019
Date Effective	May 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP211

Description

Carglumic acid (Carbaglu) is an orally administered carbamoyl phosphate synthetase 1 (CPS 1) activator.

Length of Authorization

- Initial:
  - i. Acute hyperammonemia due to NAGS deficiency: 12 months
  - ii. Chronic hyperammonemia due to NAGS deficiency: 12 months
  - iii. Acute hyperammonemia due PA or MMA: 7 days
- Renewal:
  - i. Acute hyperammonemia due to NAGS deficiency: No renewal
  - ii. Chronic hyperammonemia due to NAGS deficiency: 12 months
  - iii. Acute hyperammonemia due to PA or MMA: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
carglumic acid (generic Carbaglu)	Adjunctive therapy for acute hyperammonemia due to NAGS deficiency	200 mg tablet	250 mg/kg/day
	Maintenance therapy for chronic hyperammonemia due to NAGS deficiency		100 mg/kg/day
	Adjunctive therapy for acute hyperammonemia due to PA or MMA		≤15 kg: 150 mg/kg/day >15 kg: 3.3 g/m^2/day
carglumic acid (Carbaglu)	Adjunctive therapy for acute hyperammonemia due to NAGS deficiency	200 mg tablet	250 mg/kg/day
	Maintenance therapy for chronic hyperammonemia due to NAGS deficiency		100 mg/kg/day
	Adjunctive therapy for acute hyperammonemia due to PA or MMA		≤15 kg: 150 mg/kg/day >15 kg: 3.3 g/m^2/day

Initial Evaluation

I. **Carglumic acid (Carbaglu)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a metabolic disease specialist; **AND**

B. Documentation of member's weight within the past three months; **AND**
C. Documentation of baseline ammonia level indicating member has hyperammonemia (ammonia level is above the upper limit of normal based on member's age); **AND**
D. Treatment with generic carglumic acid (generic for Carbaglu) has been ineffective, contraindicated, or not tolerated; **AND**
E. A diagnosis of one of the following:
    1. **Hepatic enzyme N-acetylglutamate synthase (NAGS) deficiency**; **AND**
        i. Diagnosis is confirmed by mutation of the *NAGS* gene via molecular genetic testing; **AND**
        ii. The request is for acute treatment of hyperammonemia; **OR**
        iii. The request is for chronic treatment of hyperammonemia; **OR**
    2. **Propionic acidemia (PA) or methylmalonic acidemia (MMA); AND**
        i. The request is for acute management of hyperammonemia; **AND**
        ii. Diagnosis is confirmed by enzymatic, biochemical, or genetic testing; **AND**
        iii. Documentation of member's height or body surface area (BSA) within the past three months if member's weight is above 15 kg

II. Carglumic acid (Carbaglu) is considered investigational when used for all other conditions, including but not limited to:
A. Chronic treatment (use beyond 7 days) of hyperammonemia due to MMA/PA
B. Carbamoyl-Phosphate Synthase I Deficiency
C. Ornithine Carbamoyltransferase Deficiency
D. Other Urea Cycle disorders

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 **chronic hyperammonemia due to NAGS deficiency**; **AND**
IV. Documentation of member's weight within the past three months; **AND**
V. 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; **AND**
V. Treatment with generic carglumic acid (generic for Carbaglu) has been ineffective, contraindicated, or not tolerated.

Supporting Evidence

I. NAGS deficiency is a rare autosomal recessive genetic disorder caused by mutations of the NAGS gene leading to complete or partial deficiency in the enzyme N-acetylglutamate synthetase

(NAGS). The hepatic enzyme NAGS is necessary to break down nitrogen in the body. NAGS deficiency leads to accumulation of nitrogen in the form of ammonia in the blood (hyperammonemia). In most cases, onset of symptoms occurs at, or shortly following, birth (neonatal period); however, some individuals with NAGS deficiency may not exhibit symptoms until later during infancy, childhood, or even adulthood due to a partial deficiency of the NAGS enzyme. Symptoms of NAGS deficiency may include failure to thrive, poor growth, avoidance of protein from the diet, ataxia, lethargy, vomiting, and/or hypotonia. Severe manifestations include hyperammonemic coma and life-threatening complications.

II. Because NAGS deficiency is classified as an orphan disease and shares many symptoms with five other rare urea cycle disorders that result in hyperammonemia, diagnosis should be confirmed by genetic testing to verify the mutation in the *NAGS* gene. Furthermore, disease management should be by, or in consultation with, a physician who specializes in metabolic disorders.

III. Blood ammonia levels should be drawn to ensure the patient has hyperammonemia. Normal blood ammonia levels based on age are outline in the table below:

Age	Normal blood ammonia ranges
0 to 10 days (enzymatic)	170 - 341 mcg/dL
Infants and toddlers [10 days to 2 years] (enzymatic)	68 - 136 mcg/dL
Children [2 years and older]	19 - 60 mcg/dL
Adults	10 - 80 mcg/dL

IV. According to the FDA label, initial dosing for pediatric and adults with acute hyperammonemia is 100mg/kg/day to 250mg/kg/day. Maintenance for chronic hyperammonemia for pediatrics and adults is 10mg/kg/day to 100mg/kg/day. Dosage should be titrated and/or adjusted to target normal plasma ammonia level for age (referenced above).

V. The safety and efficacy of carglumic acid (Carbaglu) in the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of 23 NAGS deficiencient patients (including newborns, pediatrics, and adults) over a median period of 7.9 years (range 0.6 to 20.8 years). Due to the retrospective, unblinded, and uncontrolled nature of this review, formal statistical analyses of the data was not conducted; however, short term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days one to three, while persistence of efficacy was evaluated using long-term mean and median change in plasma ammonia level. Thirteen out of 23 patients who received carglumic acid (Carbaglu), had documented ammonia levels prior to treatment initiation and after long-term treatment. All 13 patients had abnormally elevated ammonia levels at baseline with an overall mean baseline plasma ammonia level of 271 micromol/L. For acute treatment, normal ammonia levels were attained on day three of treatment. Long-term efficacy was measured using the last reported plasma ammonia level for each patient (median length of treatment was six years; range one to 16 years). The mean and median ammonia levels were 23 micromol/L and 24 micromol/L, respectively, after a mean treatment duration of eight years.

VI. For the treatment of acute hyperammonemia due to NAGS deficiency the length of authorization is limited to 12 months. In clinical studies, doses from acute to maintenance treatment of hyperammonemia due to NAGS deficiency were reduced over time. Dose reduction to achieve a maintenance dose was undertaken within days of initiation and took anywhere from one day to 15 days for a dose reduction to be performed in majority of patents (16 of 22 patients). In five patients, it took anywhere from one month to 10 months for the dose

reduction process. Thus, it is expected that 12 months initial authorization would be sufficient to allow for titration from acute to maintence dosing and renewal would not be necessary.

VII. Methylmalonic and propionic acidemia (MMA/PA) are autosomal recessive genetic disorders characterized by accumulation of propionic acid and/or methylmalonic acid due to deficiency of methylmalonyl-CoA mutase (MUT) or propionyl-CoA carboxylase (PCC). Patients may present in the first days to weeks of life with acute deterioration of their general clinical condition, metabolic acidosis and hyperammonemia, progressing to coma and death, if untreated. Late-onset cases of MMA and PA may present at any age with a more heterogeneous clinical symptoms. Prognosis is strongly influenced by the duration of coma and peak blood ammonia concentrations and immediate treatment in consultation with a metabolic disease specialist is required. For the treatment of acute hyperammonemia due to MMA or PA, carglumic acid (Carbaglu) is expected to be administered in an inpatient setting due to the severity of presenting symptoms, need for immediate treatment and frequent monitoring.

VIII. Length of authorization is limited to seven days of treatment which is consistent with how the drug was studied in clinical trials. Acute treatment with carglumic acid (Carbaglu) should be continued until ammonia level is less than 50 micromol/L or for a maximum duration of seven days to attain a normal blood ammonia, whichever is shorter. Efficacy and safety of treating a hyperammonemic episode beyond seven days has not been established. Patients requiring re-treatment with Carglumic acid (Carbaglu) for a second hyperammonemic episode and beyond must meet initial criteria.

IX. Determination of organic acids in urine and the acylcarnitine profile in blood are the most commonly used investigations to detect MMA and PA. Enzymatic studies and/or molecular genetic analyses should be performed to confirm diagnosis. This is ideally performed in specialized laboratories.

X. Carglumic acid (Carbaglu) was studied in one randomized, double-blind, placebo-controlled, multicenter clinical trial to determine efficacy and safety in patients with hyperammonemia due to PA and MMA. Patients were randomized 1:1 to receive carglumic acid (Carbaglu) or placebo for 7 days or until hospital discharge, which ever occurred earlier. A total of 24 patients were evaluated (PA=15, MMA=9) with median age of 8 years (range 4 days to 29 years), and all receiving standard of care, including combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine. Carglumic acid (Carbaglu) was dosed at 150mg/kg/day for patients ≤15 kg or 3.3g/m^2/day for patients >15 kg administered by NG tube, G-tube, or oral syringe. Efficacy was determined based on 90 hyperammonemic episodes (42 treated with carglumic acid (Carbaglu) and 48 with placebo). Eligible hyperammonemic episodes were defined as admission to the hospital with a plasma ammonia level ≥70 µmol/L. The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level ≤50 µmol/L (normal range) or hospital discharge. The median time to reach the primary endpoint was 1.5 days in the carglumic acid (Carbaglu) arm compared to 2 days in the placebo arm (0.5 day; 95% CI: -1.2,0.1). Throughout the first three days of treatment, a higher proportion of carglumic acid (Carbaglu) treated episodes reached the primary endpoint compared to placebo-treated episodes. At least one adverse reaction was reported during the course of hyperammonemic episodes in 42.2% of hyperammonemic episodes. The most common adverse reactions (≥5%) during hyperammonemic episodes were neutropenia, anemia, vomiting, electrolyte imbalance,

decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy, and pancreatitis/increased lipase.

Investigational or Not Medically Necessary Uses

I. Carglumic acid (Carbaglu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Chronic treatment (use beyond 7 days) of hyperammonemia due to MMA/PA
      i. Carglumic acid (Carbaglu) is not FDA approved or supported by current clinical guidelines for long-term management of PA or MMA. One low evidence grade, randomized, parallel-group, open-label clinical trial studied carglumic acid (Carbaglu) for long-term treatment of PA and MMA against standard of care. Long term effectiveness was evaluated as a reduction in the number of ER admissions due to hyperammonemia. There was a 51% reduction (p=0.0095) in the number of ER admissions during the two-year observation period. No serious safety concerns reported. Additional randomized clinical trials with clinically meaningful outcomes are required to confirm signals of efficacy.
   B. Carbamoyl-Phosphate Synthase I Deficiency
   C. Ornithine Carbamoyltransferase Deficiency
   D. Other Urea Cycle disorders

References

1. Carglumic acid (Carbaglu) [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc. August 2021.
2. Center for Drug Evaluation and Research. Application Number: 22-562. Summary Review. 30 July 2009. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022562s000sumr.pdf
3. Haberle et al. Suggested guidance for the diagnosis and management of urea cycle disorders. *Orphanet Journal of Rare Diseases*. 2012, 7:32.
4. National Organization for Rare Disorders (NORD). N-Acetylgluatmate Synthetase Deficiency. Rare Disease Database. Accessed 2 December 2020. Available at: https://rarediseases.org/rare-diseases/n-acetylglutamate-synthetase-deficiency/
5. Ammonia. URMC Health Encyclopedia. Accessed 2 December 2020. Available at: https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=167&ContentID=ammonia
6. Baumgartner MR, Hörster F, Dionisi-Vici C, et al. Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia. Orphanet J Rare Dis. 2014;9:130. Published 2014 Sep 2. doi:10.1186/s13023-014-0130-8
7. Alfadhel M, Nashabat M, Saleh M, et al. Long-term effectiveness of carglumic acid in patients with propionic acidemia (PA) and methylmalonic acidemia (MMA): a randomized clinical trial. Orphanet J Rare Dis. 2021;16(1):422. Published 2021 Oct 11. doi:10.1186/s13023-021-02032-8

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication of acute treatment of hyperammonemia due to PA or MMA to initial criteria; changed initial authorization for acute hyperammonemia due to NAGS deficiency from 3 to 12 months; changed renewal authorization for acute hyperammonemia due to NAGS deficiency from 12 months to no renewal; updated supporting evidence section and experimental and not medically necessary sections.	05/2022

Added criteria of a trial and failure of generic Carbaglu prior to using branded product	12/2021
Transitioned criteria to policy format; Added requirement for weight documentation and supporting evidence section.	12/2020
Criteria created	12/2015

cenegermin-bkbi (Oxervate®)

UMP POLICY

Policy Type: PA Pharmacy Coverage Policy: UMP013

Description

Cenegermin-bkbj (Oxervate) is a recombinant human eye growth factor ophthalmic solution indicated for the treatment of neurotrophic keratitis.

Length of Authorization

- Initial: Eight weeks
- Renewal: Cannot Be Renewed

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit*
cenegermin-bkbj (Oxervate)	Neurotrophic keratitis	0.002% (20 mcg/mL) vial	56mL per 56 days, per eye

**Quantity limit of 56 mL per 56 days (28 mL/28 days) is sufficient to treat one eye. If both eyes are affected/require treatment, allowance of 112 mL per 56 days (56 mL/28 days) can occur. Treatment is once per lifetime.*

Initial Evaluation

I. **Cenegermin-bkbj (Oxervate)** may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, an ophthalmologist; **AND**
   B. A diagnosis of Neurotropic Keratitis; **AND**
   C. Antibiotic drops in combination with preservative-free artificial tears has been ineffective, contraindicated, or not tolerated; **AND**
   D. Member has Stage 2 (persistent epithelial defect) or Stage 3 (corneal ulceration, corneal perforation, or corneal stromal melting) disease; **AND**
      1. For Stage 2 disease: Therapeutic contact lens (scleral lens) have been ineffective, contraindicated, or are not tolerated; **AND**
   E. Member has NOT received prior therapy with cenegermin-bkbj (Oxervate) in the requested eye in their lifetime.

II. Cenegermin-bkbj (Oxervate) is considered investigational when used for all other conditions, including but not limited to:
   A. Treatment duration longer than 8 weeks

Renewal Evaluation

I. Product not eligible for renewal

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Supporting Evidence

I. Neurotrophic keratitis (NK) is a rare, degenerative disease of the cornea caused by damage to the trigeminal nerve, which results in reduction/loss of corneal sensitivity, epithelium breakdown, decreased corneal healing, ulceration, melting, and perforation. NK severity is divided into three stages.
   - Stage 1: characterized by epithelial irregularity most commonly in the form of punctate keratopathy without epithelial defect.
   - Stage 2: defined by recurrent or persistent epithelial defects (PED) usually oval in shape and its margins are characteristically smooth and rolled due to impaired epithelial healing. Descemet's membrane folds and stromal edema may be observed.
   - Stage 3: characterized by stromal involvement that appears as a stromal corneal ulcer and stromal edema and infiltrates; this may result in perforation and/or corneal thinning due to stromal melting.

II. The goal of therapy is to prevent progression of corneal damage and promote healing of the corneal epithelium. Treatment of NK is based on disease severity; however, use of preservative-free artificial tears may help improve the corneal surface at all stages of disease severity. Topical antibiotic eye drops are recommended in eyes with NK at stages 2 and 3 to prevent infection. Nonpharmacological treatments for NK include therapeutic corneal or scleral contact lenses in the event of PED to promote corneal epithelial healing. Surgical treatments are reserved for refractory cases.

III. Cenegermin-bkbj (Oxervate) was studied in two 8-week, phase II multi-center, randomized, double blind, placebo controlled clinical trials (Study NGF0212 (REPARO) and Study NGF0214) in adult patients with Stage 2 or Stage 3 NK who were refractory to 1 or more conventional nonsurgical treatments. In NGF0212 72% of patients treated with cenegermin-bkbj (Oxervate) achieved complete corneal healing at week 8, as well as 65.2% of patients in Study NGF0214. In patients who were healed after 8 weeks of treatment, recurrences occurred in approximately 20% of patients in Study NGF0212 and 14% of patients in Study NGF0214. Retreatment following recurrence was not assessed in either study.

IV. Efficacy of cenegermin-bkbj (Oxervate) beyond a single 8-week course of treatment or repeat treatment has not been evaluated.

V. Cenegermin-bkbj (Oxervate) is packaged in a box of #7 x 1 mL vials and is dosed to a maximum of 1 vial (1 mL) per day for 8 weeks (56 days) per treated eye. If both eyes are being treated, the patient will require two vials (2 mL) each day.

Investigational or Not Medically Necessary Uses

I. Neurotrophic Keratitis
   A. Treatment beyond the initial 8 week duration is considered experimental and investigational due to lack of studies to demonstrate efficacy beyond a single eight week course of treatment.

References

1. Oxervate [Prescribing Information]. Boston, MA: Dompé US, Inc. October 2019.
2. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neutrophic keratitis. *Opthalmology.* 2018;125(9):1332-1343.
3. Shaheen B, Bakir M, Jain S. Corneal nerves in health and disease. *Surv Opthalmol.* 2014;59(3):263-285.
4. Mantelli F, Nardella C, Tiberi E, et al. Congenital corneal anesthesia and neurotrophic keratitis: diagnosis and management. *Biomed Res Int.* 2015;2015:805876. Epub Sept. 16, 2015.
5. Semeraro F, Forbice E, Romano V, et al. Neurotrophic keratitis. *Opthalmologica*. 2014;231(4):191-197.
6. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Opthalmol.* 2014;8:571-579.
7. An Evidence based Approach to the Diagnosis and Treatment of Neurotrophic Keratopathy. CME monograph. Johns Hopkins School of Medicine. March 2020. Available at: https://hopkinscme.cloud-cme.com/assets/hopkinscme/Presentations/28879/28879.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Clarified renewal language to confirm that this medication cannot be renewed	01/2024
Clarification of QL differences when treating one versus both eyes.	11/2022
Removal of requirement "lack of active ocular infection (bacterial, viral, fungal, or protozoal) and lack of current severe blepharitis and/or severe meibomian gland disease". Removal of "documentation of cause not due to infective or autoimmune keratitis". Removal of required history of use of a topical collagenase inhibitor as this is specific to the management of stromal melting. Broke down requirement of therapeutic contact lens to be specific to Stage 2 NK. Additional requirement assuring member has not received treatment with Oxervate in their lifetime. Updates to supporting evidence.	04/2021
Policy created	01/2019

cholic acid (Cholbam®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP089

Description

Cholic acid (Cholbam) is an orally administered bile acid to help maintain bile acid homeostasis.

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
cholic acid (Cholbam)	50 mg capsules	Single Enzyme Defects (SEDs)	240 capsules/30 days	187995
	250 mg capsules	Peroxisomal disorders	240 capsules/30 days	187996

Initial Evaluation

I. Cholic acid (Cholbam) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a hepatologist or gastroenerologist; **AND**
   B. Member has **ALL** the following baseline lab values completed before initiation of therapy and continued monitoring when clinically appropriate:
      1. Aspartate aminotransferase test (AST)
      2. Alanine transaminase (ALT)
      3. Gamma-glutamyl transferase (GGT)
      4. Alkaline phosphate
      5. Bilirubin
      6. International normalized ratio (INR); **AND**
   C. A diagnosis of one of the following:
      1. **Single Enzyme Defects (SEDs); AND**
         i. Member has ONE of the following SEDs:
            a. 3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3β-HSD) deficiency
            b. Delta4-3 oxosteroid 5-beta-reductase, also known as aldoketoreductase (AKR1D1) deficiency
            c. Cerebrotendinous xanthomatosis (CTX)
            d. Alpha-methylacyl-CoA racemase (AMACR) deficiency

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

e. Sterol 27-hydroxylase (CYP27A1) deficiency
f. Smith-Lemli-Opitz; **AND**

ii. The request is for bile acid synthesis disorder due to one of the SEDs diagnosis above; **OR**

2. **Peroxisomal Disorders (PD); AND**

i. Member has ONE of the following peroxisomal disorders:
a. Neonatal Adrenoleukodystropyhy
b. Generalized Peroxisomal Disorder
c. Refsum Disease
d. Zellweger Syndrome
e. Peroxisomal Disorder, Type Unknown; **AND**

ii. Member exhibits manifestation of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption; **AND**

iii. Member will be using cholic acid (Cholbam) as adjunctive treatment

II. Cholic acid (Cholbam) is considered investigational when used for all other conditions, including but not limited to:
A. Extrahepatic manifestation of bile acid synthesis disorders due to SEDs or PDs
B. Familial hypertriglyceridemia without the diagnosis of SEDs or PDs

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.

Supporting Evidence

I. For the indication of single enzyme defects (SEDs), cholic acid (Cholbam) was studied in two clinical trials. Trial 1 was a non-randomized, open-label, single-arm trial in 50 patients over an 18 year period; trial 2 was an extension trial with 33 patients enrolled. Response to cholic acid (Cholbam) treatment was assessed with the following end points: ALT or AST values reduced to less than 50 U/L or baseline levels reduced by 80%, total bilirubin values reduced to less than or equal to 1 mg/dL, no evidence of cholestasis on liver biopsy, body weight increased by 10% or stable at greater than the 50th percentile, and survival for greater than 3 years on treatment or alive at the end of Trial 2. Regarding the 44 patients that were able to be measured at the end of the study, 28 patients (64%) were responders. Attrition information was limited.
II. For the indication of preoxisomal disorders (PDs) cholic acid (Cholbam) was studied in two clinical trials. Trial 1 was an open-label, single-arm trial in 29 patients followed over an 18 year period; while trial 2 was an extension trial with 12 patients enrolled. Response to cholic acid (Cholbam) treatment was assessed with the following end points: ALT or AST values reduced to less than 50 U/L or baseline levels reduced by 80%, total bilirubin values reduced to less than or equal to 1 mg/dL, no evidence of cholestasis on liver biopsy, body weight increased by 10% or

stable at greater than the 50th percentile, and survival for greater than 3 years on treatment or alive at the end of Trial 2. Of the 24 patients that were able to be measured at the end of the study, 11 patients (46%) were responders. Attrition information was limited.

III. Initial approval duration of three months allows for appropriate follow up with the prescriber per FDA label for cholic acid (Cholbam). It is then recommended to monitor AST, ALT, GGT, alkaline phosphatase, bilirubin and INR every month for the first 3 months, every 3 months for the next 9 months, every 6 months for the next three years, and annually for the remainder of the treatment.

Investigational or Not Medically Necessary Uses

I. Extrahepatic manifestation of bile acid synthesis disorders due to SEDs or PDs
   A. Cholic acid (Cholbam) has not been evaluated for safety and efficacy in the setting of extrahepatic manifestations.

II. Familial hypertriglyceridemia without the diagnosis of SEDs or PDs
   A. Although cholic acid (Cholbam) has an approved dosing regimen for concomitant familial hypertriglyceridemia, the safety and efficacy for patients diagnosed with familial hypertriglyceridemia without SEDs or PDs hasnot yet been evaluated.

References

1. Cholbam [Prescribing Information]. San Diego, CA: Manchester Pharmaceuticals, Inc. January 2016.

Policy Implementation/Update:

Date Created	April 2015
Date Effective	April 2015
Last Updated	
Last Reviewed	10/2019

Action and Summary of Changes	**Date**
Criteria was transitioned into policy. In this transition process, the following updates were made: addition of quantity limit, initial approval duration was changed from one year to three months following label recommendation for appropriate monitoring, renewal criteria and duration was added, supporting evidence was added, and investigational indications were added.	10/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP014

Description

The following biologics and biologic response modifiers are utilized in multiple chronic inflammatory disease states. Most of these agents target cytokines or other inflammatory mediators that are elevated in patients with such disease states. The purpose of this policy is to ensure the appropriate use of these agents.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Medications Included in this Policy

Indication	Medications
Ankylosing Spondylitis	• adalimumab (Humira®) • bimekizumab (Bimzelx®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • golimumab (Simponi®/Simponi Aria®) • ixekizumab (Taltz®) • secukinumab (Cosentyx®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Adolescent Plaque Psoriasis	• ixekizumab (Taltz®)
Behcet Syndrome – ulcer of the mouth	• apremilast (Otezla/Otezla XR®)
Crohn's Disease	• adalimumab (Humira®) • certolizumab (Cimzia®) • guselkumab (Tremfya®) • risankizumab (Skyrizi®)

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

	• ustekinumab (Stelara®) • vedolizumab SC (Entyvio®) • mirikizumab (Omvoh®) • infliximab-dyyb (Zymfentra®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-auub (Wezlana) • ustekinumab-ttwe (Pyzchiva)
Cryopyrin-Associated Periodic Syndromes (CAPS) (including Chronic Infantile Neurological, Cutaneous and Articular Syndrome (CINCA) or Neonatal-Onset Multisystem Inflammatory Disease (NOMID))	• anakinra (Kineret®)
Cryopyrin-Associated Periodic Syndromes (CAPS) (including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS))	• rilonacept (Arcalyst®)
Enthesitis-Related Arthritis	• secukinumab (Cosentyx®)
Familial Mediterranean Fever (off-label)	• anakinra (Kineret®)
Giant Cell Arteritis	• tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®)
Hidradenitis Suppurativa	• adalimumab (Humira®) • bimekizumab (Bimzelx®) • secukinumab (Cosentyx®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™)

	Non-preferred biosimilars: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Hyperimmunoglobulin D Syndrome/ Mevalonate Kinase Deficiency (HIDS/MKD) (off-label)	• anakinra (Kineret®)
Non-radiographic Axial Spondyloarthritis	• bimekizumab (Bimzelx®) • certolizumab (Cimzia®) • ixekizumab (Taltz®) • secukinumab (Cosentyx®)
Polyarticular Juvenile Idiopathic Arthritis	• abatacept (Orencia®) • adalimumab (Humira®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • sarilumab (Kevzara®) • tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Psoriatic Arthritis	• abatacept (Orencia®) • adalimumab (Humira®) • apremilast (Otezla/Otezla XR®) • bimekizumab (Bimzelx®) • certolizumab (Cimzia®)

	• etanercept (Enbrel®) • golimumab (Simponi®/Simponi Aria®) • guselkumab (Tremfya®) • ixekizumab (Taltz®) • risankizumab (Skyrizi®) • secukinumab (Cosentyx®) • ustekinumab (Stelara®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-ttwe (Pyzchiva) • ustekinumab-auub (Wezlana)
Pediatric Crohn's Disease	• adalimumab (Humira®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Pediatric Ulcerative Colitis	• adalimumab (Humira®)

	Preferred biosimilars: • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Pediatric Plaque Psoriasis	• apremilast (Otezla/Otezla XR®) • ustekinumab (Stelara®) • ustekinumab-auub (Wezlana) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) • ustekinumab-ttwe (Pyzchiva)
Pediatric Psoriatic Arthritis	• secukinumab (Cosentyx®) • apremilast (Otezla/Otezla XR®) • ustekinumab (Stelara®) • ustekinumab-auub (Wezlana) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) • ustekinumab-ttwe (Pyzchiva)
Plaque Psoriasis	• adalimumab (Humira®) • apremilast (Otezla/Otezla XR®) • brodalumab (Siliq®) • bimekizumab (Bimzelx®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • guselkumab (Tremfya®) • ixekizumab (Taltz®) • risankizumab (Skyrizi®) • secukinumab (Cosentyx®) • ustekinumab (Stelara®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™)

	• ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-auub (Wezlana) • ustekinumab-ttwe (Pyzchiva)
Polymyalgia Rheumatica	• sarilumab (Kevzara®)
Rheumatoid Arthritis	• abatacept (Orencia®) • adalimumab (Humira®) • anakinra (Kineret®) • certolizumab (Cimzia®) • etanercept (Enbrel®) • golimumab (Simponi®/Simponi Aria®) • sarilumab (Kevzara®) • tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)
Recurrent Pericarditis	• rilonacept (Arcalyst®)
Systemic Juvenile Idiopathic Arthritis	• anakinra (Kineret®) (Off Label) • tocilizumab (Actemra®)

	• tocilizumab-aazg (Tyenne®)
Systemic Sclerosis-Associated Interstitial Lung Disease	• tocilizumab (Actemra®) • tocilizumab-aazg (Tyenne®)
Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) (off-label)	• anakinra (Kineret®)
Ulcerative Colitis	• adalimumab (Humira®) • golimumab (Simponi®/Simponi Aria®) • guselkumab (Tremfya®) • risankizumab (Skyrizi®) • ustekinumab (Stelara®) • ozanimod (Zeposia®) • vedolizumab SC (Entyvio®) • mirikizumab (Omvoh®) • etrasimod (Velsipity™) • infliximab-dyyb (Zymfentra®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) • ustekinumab-stba (Steqeyma) • ustekinumab-kfce (Yesintek) • ustekinumab-aekn (Selarsdi) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®) • adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi) • ustekinumab-auub (Wezlana) • ustekinumab-ttwe (Pyzchiva)
Uveitis/Panuveitis	• adalimumab (Humira®) **Preferred biosimilars:** • adalimumab-adaz (Adalimumab-ADAZ) • adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: • adalimumab-aacf (Idacio®) • adalimumab-aaty (Yuflyma®) • adalimumab-adaz (Hyrimoz®) • adalimumab-adbm (Cyltezo®)

	• adalimumab-afzb (Abrilada™) • adalimumab-aqvh (Yusimry™) • adalimumab-atto (Amjevita™) • adalimumab-fkjp (Hulio™) • adalimumab-fkjp (Adalimumab-FKJP) • adalimumab-ryvk (Simlandi)

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 policy 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 TNF-alpha blockers such as adalimumab in combination with other biologics, such as anakinra or abatacept, has demonstrated and increases risk of serious infection with insufficient evidence for added benefit. Per product labeling, use of concomitant biologics is not recommended as there is insufficient data to support this. Similarly, non-biologic small molecules such as tofacitinib and baricitinib have not been studied sufficiently with other biologic disease-modifying antirheumatic drugs (DMARDs) to safely recommend 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 these criteria.

Rheumatoid Arthritis

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), tocilizumab-aazg (Tyenne), or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. 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.).

II. **Certolizumab (Cimzia)** may be considered medically necessary when the following criteria are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with <u>two</u> of the following has been ineffective, or not tolerated, or <u>all</u> are contraindicated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], tocilizumab-aazg (Tyenne), etanercept (Enbrel), upadacitinib (Rinvoq), or tofacitinib (Xeljanz/Xeljanz XR).

III. **Abatacept (Orencia), anakinra (Kineret), golimumab (Simponi), sarilumab (Kevzara), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), tocilizumab-aazg (Tyenne), certolizumab (Cimzia), upadacitinib (Rinvoq), and tofacitinib (Xeljanz/Xeljanz XR) have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated

IV. **Brand Humira or Brand Actemra** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. If the request is for brand Humira:
            a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
         ii. If the request is for brand Actemra:
            a. tocilizumab-aazg (Tyenne) has been tried; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), certolizumab (Cimzia), tocilizumab-aazg (Tyenne), upadacitinib (Rinvoq), and tofacitinib (Xeljanz/Xeljanz XR)

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/Otezla XR, Xeljanz, Olumiant, etc.); **AND**
    A. If the request is for **Brand Humira or Brand Actemra**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. 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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. The request is for Brand Humira; **AND**
                a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
            ii. The request is for Brand Actemra; **AND**
                a. tocilizumab-aazg (Tyenne) has been tried; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the

reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The agents listed above are approved for adult patients with rheumatoid arthritis (RA) based on safety and efficacy data from randomized-controlled trials.

III. 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).

IV. The 2019 European League Against Rheumatism (EULAR) guidelines follow similar recommendations to the 2021 ACR guidelines, and state that patients who have failed one bDMARD or tsDMARD may switch to an agent from the same class. Studies have demonstrated that primary TNF non-responders have responded to other agents of the same mechanism of action.

V. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

VI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

VII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
7. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
8. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
9. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), tocilizumab-aazg (Tyenne)**, **or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** when the following is 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.

II. **Certolizumab (Cimzia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with <u>two</u> of the following has been ineffective or not tolerated, or <u>all</u> are contraindicated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), tocilizumab-aazg (Tyenne), tofacitinib (Xeljanz), or upadacitinib (Rinvoq).

III. **Abatacept (Orencia), sarilumab (Kevzara), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Request is for abatacept (Orencia) or non-preferred adalimumab biosimilars; **OR**
      1. Request is for sarilumab (Kevzara); **AND**
      2. Member weighs 63 kilograms or more; **AND**

C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), tocilizumab-aazg (Tyenne), certolizumab (Cimzia), upadacitinib (Rinvoq), and tofacitinib (Xeljanz) have been ineffective, contraindicated, or not tolerated; **AND**
    1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated

IV. **Brand Humira or Brand Actemra** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(B) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
    1. The member experienced a documented intolerance to the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. The request is for Brand Humira; **AND**
            a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
        ii. The request is for Brand Actemra; **AND**
            a. tocilizumab-aazg (Tyenne) has been tried; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **AND**
D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), tocilizumab-aazg (Tyenne), certolizumab (Cimzia), upadacitinib (Rinvoq), and tofacitinib (Xeljanz)

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., Humira, Xeljanz, Infliximab, etc.); **AND**
    A. If the request is for **Brand Humira**: 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 biosimilar; **AND**
    B. 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
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. The request is for Brand Humira; **AND**
                a. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
            ii. The request is for Brand Actemra; **AND**
                a. tocilizumab-aazg (Tyenne) has been tried; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic

treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

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. Adalimumab (Humira), etanercept (Enbrel), abatacept (Orencia) and tocilizumab (Actemra) are approved for pediatric patients greater than two years of age with PJIA based on safety and efficacy data from randomized-controlled trials.

IV. 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.

V. 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 patients currently on DMARD or oral glucocorticoid.

VI. Sarilumab (Kevzara) is approved for active PJIA in pediatric patients who weigh 63 kg or greater. Use of sarilumab (Kevzara) in this patient population is supported by evidence from adequate and well-controlled studies of sarilumab (Kevzara) in adults with RA, pharmacokinetic data from adult patients with RA, and a pharmacokinetic, pharmacodynamic, dose-finding, and safety study in pediatric patients with PJIA 2 years of age and older. Sarilumab (Kevzara) is not approved in pediatric patients weighing less than 63 kg because of the lack of an appropriate dosage form nor is the safety and efficacy established in those under 2 years of age.

VII. In September 2024, certolizumab (Cimzia) was approved in PJIA for patients aged two and older. This approval was based on the efficacy of adult patients in RA combined with pharmacokinetic studies in pediatrics. Additionally, an open-label study (PASCAL) was assessed in 193 patients aged two to 17 after failure of biologic/non-biologic dmard. Efficacy was assessed as secondary endpoints at week 24, PASCAL was primarily a PK/safety study; the results were consistent with adult RA study patients. Certolizumab (Cimzia) is given as weight-based dosing for this indication.

VIII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

IX. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

X. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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. 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.

3. 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.
4. 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
5. Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis. 2020 [PROPEL Study] (NCT02592434)
6. Upadactinib (Rinvoq/Rinvoq LQ) [Prescribing information]. North Chicago, IL; AbbVie Inc. Updated April 2024
7. Kevzara (sarilumab). Package Insert. Sanofi; Bridgewater, NJ, 08807. Updated June 2024.
8. Cimzia (certolizumab). Package Insert. UCB, Inc; Smyrna, GA 30080. Updated September 2024.
9. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
10. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
11. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
12. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Enthesitis-Related Arthritis (ERA)

Initial Evaluation

I. **Secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Enthesitis-Related Arthritis (ERA)** when the following is 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.

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 enthesitis-related arthritis (ERA) or another auto-immune condition (e.g., Humira, Xeljanz, Infliximab, etc.).

Supporting Evidence

I. Enthesitis-related arthritis (ERA) is a subset of juvenile idiopathic arthritis (JIA) and is characterized primarily by inflammation of the entheses, or connective tissue between tendon/ligament and bone, and commonly affects sacroiliac or lumbosacral joints. Other subsets of JIA include PJIA, 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.

II. Secukinumab (Cosentyx) was approved for pediatric patients aged four years or older with ERA based on safety and efficacy from a phase 3 study (JUNIPERA) of children aged 2-17 years with a diagnosis of active ERA or juvenile psoriatic arthritis with an inadequate response or intolerance to at least 1 NSAID and at least 1 DMARD. The majority (67.6% of juvenile psoriatic arthritis, 63.5% of ERA) of patients were taking concomitant methotrexate throughout the study. The primary endpoint was time to flare over a 92-week period, which was met with a statistically significant longer time to flare in the secukinumab group compared to placebo group for both indications; risk of flare was reduced by 53% in ERA (HR 0.47, 95% CI 0.17-1.32) and 85% in juvenile psoriatic arthritis (HR 0.15, 95% CI 0.04-0.56). Improvements in the secondary endpoint JIA ACR 30/50/70/90 were also seen in the intervention group relative to placebo. No new safety signals were discovered, and adverse effects were consistent with the established safety profile of secukinumab.

III. The 2019 ACR JIA guidelines provide recommendations for enthesitis, which include ERA, psoriatic arthritis, and undifferentiated arthritis, all of which fall under the JIA umbrella. For patients with ERA, initial therapy with an NSAID is recommended. In the second-line setting, ACR provides a conditional recommendation for TNF inhibitors over DMARD, though this is based on low-quality evidence; this recommendation is rooted in retrospective cohort and phase 3 studies of etanercept and adalimumab for several different subtypes of JIA, including ERA, which provided mixed signals that biologics are more effective than placebo or no comparator, but the majority of included patients had previously been treated with at least one NSAID and DMARD. It has also been suggested that methotrexate is not as effective at managing axial manifestations of ERA. However, DMARDs remain a viable first-line option for ERA patients given their well-established efficacy and safety profile, especially in those with mild disease or concomitant active polyarthritis. Age-appropriate biologics approved for ERA, PJIA or juvenile psoriatic arthritis should be reserved for subsequent therapy.

IV. While other biologics have been evaluated for use in ERA or other JIA subtypes, only secukinumab (Cosentyx) is FDA-approved for ERA. Notably, etanercept and adalimumab have undergone one phase 3 study each in ERA patients but neither have pursued FDA approval. In a 12-week randomized, double-blind study of ERA patients age 6-18 years (n=46) followed by a 180-week open label single-arm extension, adalimumab was found to provide a statistically significant greater reduction in the number of active joints with arthritis at week 12 compared to placebo, but the majority of secondary endpoints, including ACR 30/50/70/90, were not met. In a 12-week single-arm open-label study of JIA patients, including ERA, extended oligoarticular JIA and PsA patients age 12-17 years (n=127) with an 86-week single-arm extension, a greater proportion of patients treated with etanercept achieved JIA ACR30 compared to historical placebo data. No new safety concerns arose during studies. At this time, the quality of these data are considered low due to small sample size, single-arm open-label study design, and lack of clinically meaningful endpoints being met.

References

1. 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;71(6):846-863.

2. Ruperto N, Foeldvari I, Alexeeva E, et al. Lb0004 efficacy and safety of secukinumab in enthesitis-related arthritis and juvenile psoriatic arthritis: primary results from a randomised, double-blind, placebo-controlled, treatment withdrawal, phase 3 study(Junipera). *Annals of the Rheumatic Diseases*. 2021;80(Suppl 1):201-202.
3. UpToDate, Inc. Spondyloarthritis in children. UpToDate [database online]. Waltham, MA. Last updated December 4, 2020. Available at uptodate.com. Accessed February 4, 2022.
4. Burgos-Vargas R, Tse SML, Horneff G, et al. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. *Arthritis Care Res (Hoboken).* 2015;67(11):1503-1512.
5. Horneff G, Burgos-Vargas R, Constantin T, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (Week 12) of the CLIPPER study. *Ann Rheum Dis*. 2014;73(6):1114-1122.

Systemic Juvenile Idiopathic Arthritis (SJIA)

Initial Evaluation

I. **Tocilizumab-aazg (Tyenne)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **active SJIA** when the following are met:
      1. Treatment with at least one NSAID (e.g., ibuprofen, naproxen, indomethacin, meloxicam, celecoxib, etc.) or glucocorticoid (i.e., prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Patient has severe active disease as indicated by one of the following:
         i. Suspected early macrophage activating syndrome (MAS)
         ii. Disabling polyarthritis
         iii. Serositis

II. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with tocilizumab-aazg (Tyenne) has been ineffective, contraindicated, or not tolerated.

III. **Abatacept (Orencia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with anakinra (Kineret) AND tocilizumab-aazg (Tyenne) has been ineffective, contraindicated, or not tolerated.

IV. **Brand Actemra** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) 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 a biosimilar product; **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**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: tocilizumab-aazg (Tyenne), anakinra (Kineret), and abatacept (Orencia).

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**
I. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat juvenile idiopathic arthritis or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, Infliximab, etc.); **AND**
    A. If the request is for **Brand Actemra**: 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 biosimilar; **AND**
    B. 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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
            i. tocilizumab-aazg (Tyenne) has been tried; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or

more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:

i. Was life-threatening; **OR**
ii. Required hospitalization; **OR**
iii. Required intervention to prevent impairment or damage

Supporting Evidence

II. Anakinra (Kineret) does not have FDA approval for SJIA but did gain approval recently by the European Medicines Agency for this indication in 2018. A prospective trial examined 42 children with new-onset disease after no response to a seven-day trial of NSAIDs. Rapid improvement was seen, with inactive disease noted in 55% and 71% of patients at one and three months, respectively. A similar rate of response was seen in a small RCT (ANAJIS) to that seen in the tocilizumab trial and is described below in terms of ACR30.

III. Tocilizumab is approved for treatment of active SJIA in patients two years and older. In a RCT of 112 children with SJIA for greater than six months, who had an inadequate response to NSAIDs and glucocorticoids, tocilizumab patients were more likely to achieve JIA ACR30 response by week 12 compared to placebo (85% vs 24%, $p<0.001$).

IV. The SJIA guidelines updated in 2013 by the ACR note that NSAIDs are recommended as an initial treatment approach. However, based off expert opinion, monotherapy is inappropriate for patients with an MD global assessment score of 5 or greater (0-10 scale), indicating severe disease. Likewise, it is noted that macrophage activation syndrome (MAS) which occurs in approximately 10% of SJIA patients, is a severe, life-threatening condition and delay in IL-1 or IL-6 inhibitor therapy should not occur in this scenario. Anakinra (Kineret) is recommended as an initial treatment option in patients with severely active disease, as well as for patients with continued disease activity after treatment with glucocorticoid or NSAID monotherapy. For those patients who have tried both anakinra (Kineret) and tocilizumab (Actemra) sequentially, abatacept (Orencia) is recommended based off expert opinion. A subset of 37 children with systemic JIA was examined in comparison to placebo in a RCT. After four months of treatment in the initial lead-in period, 24 of 37 patients (65%) treated with abatacept had a ACR30 response, which was similar to response rates seen in patients included with other JIA subtypes.

V. TNF inhibitors demonstrate greater efficacy in patients with nonsystemic JIA compared to SJIA. For instance, a study of 45 children who had systemic symptoms at the start of TNF inhibitor therapy noted lower rates of remission and a high frequency of disease flare (24% and 45%, respectively).

VI. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

VII. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a

rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

VIII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum*. 2013;65(10):2499-2512.
2. UpToDate, Inc. Systemic juvenile idiopathic arthritis: treatment. UpToDate [database online]. Waltham, MA. Last updated April 2, 2019. Available at: http://www.uptodate.com/home/index.html.
3. De benedetti F, Brunner HI, Ruperto N, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med.* 2012;367(25):2385-2395.
4. Ter haar NM, Van dijkhuizen EHP, Swart JF, et al. Treat-to-target using first-line recombinant interleukin-1 receptor antagonist monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five year follow-up study. *Arthritis Rheumatol*. 2019.
5. Quartier P, Allantaz F, Cimaz R, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis.* 2011;70(5):747-754.
6. Russo RA, Katsicas MM. Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents. *J Rheumatol.* 2009;36(5):1078-1082.
7. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet.* 2008;372(9636):383-391.
8. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
9. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
10. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
11. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Psoriatic Arthritis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), apremilast (Otezla/Otezla XR), secukinumab (Cosentyx), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma), risankizumab (Skyrizi), or guselkumab (Tremfya)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
   B. 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 C-reactive protein (CRP) or erythrocyte sedimentation rate (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

II. **Certolizumab (Cimzia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with <u>two</u> of the following has been ineffective or not tolerated, or <u>all</u> are contraindicated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], guselkumab (Tremfya), tofacitinib (Xeljanz/Xeljanz XR), risankizumab (Skyrizi), upadacitinib (Rinvoq), and apremilast (Otezla/Otezla XR)

III. **Abatacept (Orencia), golimumab (Simponi), ixekizumab (Taltz), bimekizumab (Bimzelx), non-preferred ustekinumab biosimilars, or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Member is 18 years of age or older; **AND**
      1. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), apremilast (Otezla/Otezla XR), secukinumab (Cosentyx), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], certolizumab (Cimzia), risankizumab (Skyrizi), guselkumab (Tremfya), tofacitinib (Xeljanz/Xeljanz XR), and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated; **AND**
         i. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars (adalimumab-bwwd (Hadlima) and

adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, contraindicated, or not tolerated; **OR**

ii. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars (ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)) have been ineffective, contraindicated, or not tolerated; **OR**

C. Member is two to five years of age; **AND**

1. Treatment with secukinumab (Cosentyx) has been ineffective, contraindicated, or not tolerated; **OR**

D. Member is six to 17 years of age; **AND**

1. Treatment with secukinumab (Cosentyx) and ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], and apremilast (Otezla/Otezla XR) have been ineffective, contraindicated, or not tolerated.

IV. **Brand Humira or brand Stelara** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A)-I(B) above are met; **AND**

B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**

i. If the request is for brand Humira, treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, contraindicated, or not tolerated; **OR**

ii. If the request is for brand Stelara, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, contraindicated, or not tolerated; **OR**

2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**

3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:

i. Was life-threatening; **OR**

ii. Required hospitalization; **OR**

iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), certolizumab (Cimzia),

apremilast (Otezla/Otezla XR), secukinumab (Cosentyx), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], guselkumab (Tremfya), tofacitinib (Xeljanz/Xeljanz XR), risankizumab (Skyrizi), and upadacitinib (Rinvoq)

**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.*

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 psoriatic arthritis or another auto-immune condition (e.g., Humira, Otezla/Otezla XR, Olumiant, etc.); **AND**
    A. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. 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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
            ii. If the request is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)]; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved for adult patients in the treatment of psoriatic arthritis based on safety and efficacy data from randomized-controlled trials. Additionally, secukinumab (Cosentyx) was approved for pediatric patients aged two years or older with psoriatic arthritis based on safety and efficacy from a phase 3 study (JUNIPERA) of children aged 2-17 years with a diagnosis of active enthesitis-related arthritis or juvenile psoriatic arthritis with an inadequate response or intolerance to at least 1 NSAID and at least 1 DMARD. See PJIA section for additional study details.

III. 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, prefer oral therapy, or have 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.

IV. According to the 2019 ACR guidelines for juvenile idiopathic arthritis (JIA), which have been described in the PJIA section, treatment of pediatric PsA is similar to adult PsA: oral DMARD as first line, TNF inhibitors or other biologics as second line. Regardless of the level of disease activity, initial therapy with a DMARD is recommended over a biologic. However, initial therapy with a biologic may be preferred for patients with risk factors for/involvement of high-risk joints (cervical spine, wrist, hip), high disease activity, and/or those judged by their physician to be at risk of disabling joint disease.

V. 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).

VI. 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). In January 2022, the latest agent, risankizumab, an IL-23 inhibitor, was approved; however, the guidelines have not been updated with regard to place in therapy for risankizumab or other IL-23 inhibitors, such as guselkumab.

VII. The 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) clinical guidelines is the latest international clinical guidance document which makes evidence-based treatment recommendations for adults with PsA, utilizing a domain-based approach, spanning six domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis and nail psoriasis.

- In patients presenting with peripheral arthritis and treatment naïve to conventional synthetic disease modifying antirheumatic drugs (csDMARDs) (methotrexate, sulfasalazine, or leflunomide), csDMARDs are strongly recommended as a first-line treatment option.
- For patients with inadequate response to csDMARDs, TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors, IL-12/23 inhibitors, JAK inhibitors, and PDE4 inhibitors are strongly recommended on the basis of high-moderate quality evidence. Based on current evidence, including head-to-head studies TNF inhibitors, IL-17 inhibitors, and JAK inhibitors are equally recommended. There are no studies comparing IL-23 inhibitors with other bDMARDs or JAK inhibitors.
- For patients with enthesitis, dactylitis, and nail psoriasis TNF inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, IL-23 inhibitors, JAK inhibitors, and PDE4 inhibitors are equally strongly recommended, while methotrexate carries a conditional recommendation for these disease manifestations. For plaque psoriasis, topical therapies, methotrexate, famarate, and bDMARDs all carry a strong recommendation.

VIII. Expanded approval of ustekinumab for active psoriatic arthritis for children and adolescents was based on data extrapolation from multiple phase 3 studies for adults and pediatric patients with moderate to severe plaque psoriasis (PSTELLAR, CADMUS, and CADMUS Jr) and multiple phase 3 studies for adults with active psoriatic arthritis (PSUMMIT I and II). Pharmacokinetic and safety data analysis in pediatric patients with active psoriasis and psoriatic arthritis are comparable to adult data in regard to pharmacokinetic concentrations and disease-medication response, with no additional safety issues present in the pediatric population (similar with no new safety signals when compared pediatric AE to adult AE rates).

IX. Expanded approval of abatacept (Orencia) and etanercept (Enbrel) in pediatric patients ages two and up for psoriatic arthritis was based on data extrapolation from studies in adult populations (PsA and RA) and pediatric patients with PJIA (and PsO for Enbrel). Observed trough concentrations were found to be generally comparable between adults and pediatric patients. Pharmacokinetic exposure is expected to be comparable between adult and pediatric patients with PsA.

X. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same

strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References:

1. 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.
2. 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.
3. Mease PJ, Gladman DD, Samad AS, et al. Design and rationale of the Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA). RMD Open. 2018;4(1):e000606.
4. UpToDate, Inc. Treatment of psoriatic arthritis. UpToDate [database online]. Waltham, MA. Last updated November 20, 2018. Available at: http://www.uptodate.com/home/index.html.
5. Deodhar A, Helliwell PS, Boehncke WH, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial [published correction appears in Lancet. 2020 Apr 4;395(10230):1114]. Lancet. 2020;395(10230):1115-1125. doi:10.1016/S0140-6736(20)30265-8
6. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial [published correction appears in Lancet. 2020 Apr 4;395(10230):1114]. Lancet. 2020;395(10230):1126-1136. doi:10.1016/S0140-6736(20)30263-4
7. Kristensen LE, Keiserman M, Papp K,et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. Ann Rheum Dis. 2022 Feb;81(2):225-231. doi: 10.1136/annrheumdis-2021-221019. Epub 2021 Dec 15. PMID: 34911706; PMCID: PMC8762015
8. Östör A, Van den Bosch F, Papp K, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. Ann Rheum Dis. 2021 Nov 23:annrheumdis-2021-221048. doi: 10.1136/annrheumdis-2021-221048. Epub ahead of print. PMID: 34815219.
9. Gossec L, Baraliakos X, Kerschbaumer A, et alEULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 updateAnnals of the Rheumatic Diseases 2020;79:700-712.
10. Leu JH, Shiff NJ, Clark M, Bensley K, Lomax KG, Berezny K, Nelson RM, Zhou H, Xu Z. Intravenous Golimumab in Patients with Polyarticular Juvenile Idiopathic Arthritis and Juvenile Psoriatic Arthritis and Subcutaneous Ustekinumab in Patients

with Juvenile Psoriatic Arthritis: Extrapolation of Data from Studies in Adults and Adjacent Pediatric Populations. Paediatr Drugs. 2022 Sep 28. doi: 10.1007/s40272-022-00533-y. Epub ahead of print. PMID: 36171515.
11. Ritchlin CT, Coates LC, McInnes IB, et al. Bimekizumab treatment in biologic DMARD-naïve patients with active psoriatic arthritis: 52-week efficacy and safety results from the phase III, randomised, placebo-controlled, active reference BE OPTIMAL study. Ann Rheum Dis. 2023;82(11):1404-1414. doi:10.1136/ard-2023-224431
12. Merola JF, Landewé R, McInnes IB, et al. Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor-α inhibitors: a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE). Lancet. 2023;401(10370):38-48. doi:10.1016/S0140-6736(22)02303-0
13. Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021 [published correction appears in Nat Rev Rheumatol. 2022 Dec;18(12):734. doi: 10.1038/s41584-022-00861-w]. Nat Rev Rheumatol. 2022;18(8):465-479. doi:10.1038/s41584-022-00798-0
14. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
15. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
16. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
17. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Ankylosing Spondylitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel) or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Ankylosing Spondylitis (Axial Spondyloarthritis)** when the following are met:
      1. High disease activity (e.g., bothersome chronic neck, back, or hip pain, peripheral joint pain, morning stiffness, fatigue, objective signs of inflammation, functional impairment, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4, Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥2.1); **AND**
      2. Treatment with at least two different Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated.

II. **Certolizumab (Cimzia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with <u>two</u> of the following has been ineffective or not tolerated, or <u>all</u> are contraindicated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), upadacitinib (Rinvoq), or tofacitinib (Xeljanz).

III. **Golimumab (Simponi), ixekizumab (Taltz), bimekizumab (Bimzelx) or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**

B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), certolizumab (Cimzia), secukinumab (Cosentyx), tofacitinib (Xeljanz), and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated; **AND**
    1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated

IV. **Brand Humira** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(B) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
    4. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**

    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **AND**
D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel), certolizumab (Cimzia), secukinumab (Cosentyx), tofacitinib (Xeljanz), and upadacitinib (Rinvoq)

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., Rinvoq, Otezla/Otezla XR, Olumiant, Infliximab, etc.); **AND**

A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

B. 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**

5. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved for adult patients in the treatment of ankylosing spondylitis based on safety and efficacy data from randomized-controlled trials.

III. Axial spondyloarthritis (SpA or axSpA) is an umbrella term which is comprised of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis (AS) is an older term and is used interchangeably with the term axial spondyloarthritis (SpA or

axSpA). AS or axSpA or SpA or r-axSpA and nr-axSpA represent two stages of the same disease: the nr-axSpA represents an earlier stage without definite radiographic sacroiliitis. In contrast, definitive radiographic changes on X-ray are present with AS. However, not all nr-axSpA patients progress to AS. Additionally, it has been shown that axSpA and nr-axSpA are largely similar with regard to burden of disease, including the presence of comorbidities, treatment received and response. Since typical signs and symptoms of SpA do not depend on the degree of SI joint damage, patients' symptoms present similarly. On average, loss of function and work impairment in nr-axSpA and AS are comparable. Both manifestations deserve the same level of treatment and care. Clinical guideline recommendations for both axSpA and nr-axSpA follow the same recommendations with variable quality of evidence.

IV. SpA is a relapsing remitting disease. When the disease is active it is characterized by chronic low back pain, swelling, and inflammation with a usual onset before 45 years of age. The disease is also commonly associated with insidious onset, fatigue, morning stiffness, improvement of symptoms with exercise, HLA-B27 positivity, elevated markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Peripheral manifestations are also possible and include peripheral arthritis, enthesitis, and dactylitis. Peripheral arthritis commonly presents as arthritis of the knees, ankles etc., enthesitis which is inflammation of entheses, (site of insertion of ligaments, tendons, joint capsule, or fascia to bone) commonly manifests as swelling at the heels, at the insertion of the Achilles tendon, or at the insertion of the plantar fascia ligament into the calcaneus, and dactylitis (sausage digits) manifests as swollen digits. Lastly, extramusculoskeletal manifestations (EMMs) are possible, which include uveitis/iritis, skin psoriasis, and inflammatory bowel disease (IBD). In patients SpA and comorbid EMMs, comorbidities often guide therapeutic choices.

V. Diagnosis of SpA is challenging which requires weighing of multiple risk factors and is based on clinical presentation in combination with laboratory and imaging tests and exclusion of other more likely diagnoses. Importantly, diagnosis is not made based on Assessment of SpondyloArthritis international society (ASAS) axSpA classification criteria, which is only used for research purposes. Although inflammatory back pain alone is not sufficient to diagnose SpA, its presence is an important initial step in preselection of patients with a high probability of SpA. Other typical features of SpA include good initial response to NSAIDs, peripheral manifestations, EMMs, positive family history, elevated lab markers such CRP and ESR, and HLA-B27 positivity. Imaging (plain radiography or X-ray) can detect sacroiliitis of the axial skeleton in patients with radiographic changes (AS). Patients that are not positive for sacroiliitis by plain imaging or X-rays can undergo MRI to detect inflammatory changes of the joints. Patients without abnormalities on imaging (X-ray or MRI) but with other SpA typical features (symptoms, lab markers, etc.) can be diagnosed with nr-axSpA.

VI. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are scoring instruments that assess disease activity when monitoring patients with SpA. ASDAS incorporates patient perspectives of their disease activity and includes CRP as an objective measure of inflammation while BASDAI reflects only the patient perspective. Both instruments incorporate questions that assess the level of fatigue, pain, swelling, discomfort, and morning stiffness. While the 2022 ASAS-EULAR clinical guidelines endorse the use of these instruments in clinical practice to determine when escalation in therapy may be needed and to determine response to treatment, the use of these instruments to determine treatment intensification or baseline disease activity is not strongly recommended in the 2019 ACR/SAA/SPARTAN guidelines. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend regular-interval use and monitoring of a validated AS disease activity measure and conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR

over usual care. The 2019 ACR/SAA/SPARTAN guidelines further note that no studies addressed the effect of routine monitoring of a disease activity measure, such as the BASDAI or the ASDAS, or acute-phase reactants on outcomes in patients with AS. In clinical settings, the use of BASDAI and ASDAS instruments is not uniformly adopted and other factors other than disease activity often play a role when making treatment decisions. Medical necessity for treatment escalation to a biologic or Janus Kinase (JAK) inhibitor requires that patients have high disease activity which may be defined by BASDAI or ASDAS scores if available or could be determined by a positive rheumatologists' opinion to escalate treatment based on prior failure of conventional therapies (e.g., NSAIDs) and a clinical exam which evaluates presence of ongoing bothersome symptoms, as well as laboratory exams that support ongoing inflammation.

VII. The 2019 ACR/SAA/SPARTAN and the 2022 ASAS-EULAR guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% patients responding). No particular NSAID has been determined to be superior in efficacy or safety and guidelines don't recommend a preferred choice. Guidelines recommend that lack of response (or intolerance) to at least two different NSAIDs at maximal doses over one month, or incomplete responses to at least two different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with Tumor Necrosis Factor (TNF) inhibitors.

VIII. For those patients with inadequate response despite continuous NSAID treatment, the 2019 ACR/SAA/SPARTAN panel recommends the use of TNF inhibitors as the preferred next choice due to experience and familiarity with their long-term safety and toxicity. Guidelines do not recommend any particular TNF inhibitor as the preferred choice. For those patients with continued active disease, the panel conditionally recommends a trial of a different TNF inhibitor over treatment with a non-TNF inhibitor in patients with secondary nonresponse to TNF inhibitor (those that initially responded and subsequently lost response over time). In patients that never responded to a first trial of a TNF inhibitor (primary nonresponse), trial of a different TNF inhibitor is <u>not</u> recommended and use of subsequent biologics of JAK inhibitors is preferred. Patients presenting with peripheral arthritis symptoms have additional treatment options before escalating to a biologic, which include sulfasalazine and local glucocorticoid (GC) injections. GC injections may also be used in patients with isolated sacroiliitis.

IX. In patients with intolerance, contraindications, or loss of efficacy with TNF inhibitors, the 2019 ACR/SAA/SPARTAN guidelines recommend IL-17A inhibitors next, followed by JAK inhibitors. 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 Rheumatoid Arthritis (RA), reflective of a JAK inhibitor class effect, or specific to tofacitinib (Xeljanz). Until more data becomes available, the 2022 ASAS-EULAR guidelines advise 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.

X. According to the 2022 ASAS-EULAR and 2019 ACR/SAA/SPARTAN guidelines, treatment decisions may differ for patients presenting with EMMs. For example, for those with SpA and comorbid uveitis/iritis, adalimumab, infliximab, golimumab, and certolizumab pegol may be preferred over etanercept as this TNF inhibitor showed contradictory results. Secukinumab was shown to be unsuccessful in patients with non-infectious uveitis while rates of uveitis flares with ixekizumab have not been well-defined. For patients with comorbid inflammatory bowel disease (IBD), TNF inhibitors are preferred (except etanercept which is not effective in IBD). Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease. Increased risks of IBD exacerbation appear to also occur with ixekizumab. For psoriasis and SpA,

guidelines suggest that IL-17 inhibitors may be preferred, however, no comparative data is available on psoriasis patients with axSpA. For the treatment of psoriasis and SpA, a product that is FDA approved for both indications is preferred.

XI. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend against the addition of sulfasalazine or methotrexate to biologic drugs and do not recommend these treatments for those with predominantly axial disease symptoms. This is based off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these agents may be considered for patients with ankylosing spondylitis with predominantly peripheral arthritis symptoms. Similar recommendations are made by the 2022 ASAS/EULAR guidelines.

XII. 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.

XIII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XIV. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XV. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. Baraliakos X, Deodhar A, van der Heijde D, et al. Bimekizumab treatment in patients with active axial spondyloarthritis: 52-week efficacy and safety from the randomised parallel phase 3 BE MOBILE 1 and BE MOBILE 2 studies. Ann Rheum Dis. 2024;83(2):199-213. Published 2024 Jan 11. doi:10.1136/ard-2023-224803
7. Deodhar A. What is non-radiographic axial spondyloarthritis? Spondylitis Association of America. Accessed October 25, 2024. https://spondylitis.org/spondylitis-plus/what-is-non-radiographic-axial-spondyloarthritis/
8. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
9. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
10. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
11. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Non-radiographic Axial Spondyloarthritis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), certolizumab (Cimzia), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **Non-radiographic Axial Spondyloarthritis** when the following are met:
      1. High disease activity (e.g., bothersome chronic neck, back, or hip pain, peripheral joint pain, morning stiffness, fatigue, objective signs or inflammation, functional impairment, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4, Ankylosing Spondylitis Disease Activity Score (ASDAS) score ≥2.1; **AND**
      2. Treatment with at least two different Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated**.**

II. **Ixekizumab (Taltz), bimekizumab (Bimzelx) or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**

B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), certolizumab (Cimzia), secukinumab (Cosentyx), and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated; **AND**
    1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(B) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **AND**
D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel), certolizumab (Cimzia), secukinumab (Cosentyx), and upadacitinib (Rinvoq)

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/Otezla XR, Xeljanz, Olumiant, Infliximab, etc.); **AND**

A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
B. 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**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Currently, certolizumab pegol, ixekizumab, secukinumab, upadacitinib, and bimekizumab are the only FDA approved agent for adults with non-radiographic axial spondyloarthritis. All FDA approved drugs were studied in Phase 3 studies which demonstrated statistically significant improvements in ASAS 40 response and other outcomes. Other TNF inhibitors are approved in Europe for this indication, have demonstrated efficacy in RCTs, and are utilized frequently in clinical practice. For instance, 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. Axial spondyloarthritis (SpA or axSpA) is an umbrella term which is comprised of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis (AS) is an older term and is used interchangeably with the term axial spondyloarthritis (SpA or axSpA). AS or axSpA or SpA or r-axSpA and nr-axSpA represent two stages of the same disease: the nr-axSpA represents an earlier stage without definite radiographic sacroiliitis. In contrast, definitive radiographic changes on X-ray are present with AS. However, not all nr-axSpA patients progress to AS. Additionally, it has been shown that axSpA and nr-axSpA are largely similar with regard to burden of disease, including the presence of comorbidities, treatment received and response. Since typical signs and symptoms of SpA do not depend on the degree of SI joint damage, patients' symptoms present similarly. On average, loss of function and work impairment in nr-axSpA and AS are comparable. Both manifestations deserve the same level of treatment and care. Clinical guideline recommendations for both axSpA and nr-axSpA follow the same recommendations with variable quality of evidence.

IV. SpA is a relapsing remitting disease. When the disease is active it is characterized by chronic low back pain, swelling, and inflammation with a usual onset before 45 years of age. The disease is also commonly associated with insidious onset, fatigue, morning stiffness, improvement of symptoms with exercise, HLA-B27 positivity, elevated markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Peripheral manifestations are also possible and include peripheral arthritis, enthesitis, and dactylitis. Peripheral arthritis commonly presents as arthritis of the knees, ankles etc., enthesitis which is inflammation of entheses, (site of insertion of ligaments, tendons, joint capsule, or fascia to bone) commonly manifests as swelling at the heels, at the insertion of the Achilles tendon, or at the insertion of the plantar fascia ligament into the calcaneus, and dactylitis (sausage digits) manifests as swollen digits. Lastly, extramusculoskeletal manifestations (EMMs) are possible, which include uveitis/iritis, skin psoriasis, and inflammatory bowel disease (IBD). In patients SpA and comorbid EMMs, comorbidities often guide therapeutic choices.

V. Per 2019 ACR/SAA/SPARTAN non-radiographic axial spondyloarthritis treatment guidelines, 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. A systematic review by Corbett et al published in 2016 demonstrated significant improvement in disease state measures such as the ASAS20 and BASDAI50 in patients with non-radiographic axial spondyloarthritis taking TNF inhibitors such as adalimumab, certolizumab pegol, etanercept, and infliximab.

VI. Diagnosis of SpA is challenging which requires weighing of multiple risk factors and is based on clinical presentation in combination with laboratory and imaging tests and exclusion of other more likely diagnoses. Importantly, diagnosis is not made based on Assessment of SpondyloArthritis international society (ASAS) axSpA classification criteria, which is only used for research purposes. Although inflammatory back pain alone is not sufficient to diagnose SpA, its presence is an important initial step in preselection of patients with a high probability of SpA. Other typical features of SpA include good initial response to NSAIDs, peripheral manifestations, EMMs, positive family history, elevated lab markers such CRP and ESR, and HLA-B27 positivity. Imaging (plain radiography or X-ray) can detect sacroiliitis of the axial skeleton in patients with

radiographic changes (AS). Patients that are not positive for sacroiliitis by plain imaging or X-rays can undergo MRI to detect inflammatory changes of the joints. Patients without abnormalities on imaging (X-ray or MRI) but with other SpA typical features (symptoms, lab markers, etc.) can be diagnosed with nr-axSpA.

VII. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are scoring instruments that assess disease activity when monitoring patients with SpA. ASDAS incorporates patient perspectives of their disease activity and includes CRP as an objective measure of inflammation while BASDAI reflects only the patient perspective. Both instruments incorporate questions that assess the level of fatigue, pain, swelling, discomfort, and morning stiffness. While the 2022 ASAS-EULAR clinical guidelines endorse the use of these instruments in clinical practice to determine when escalation in therapy may be needed and to determine response to treatment, the use of these instruments to determine treatment intensification or baseline disease activity is not strongly recommended in the 2019 ACR/SAA/SPARTAN guidelines. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend regular-interval use and monitoring of a validated AS disease activity measure and conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care. The 2019 ACR/SAA/SPARTAN guidelines further note that no studies addressed the effect of routine monitoring of a disease activity measure, such as the BASDAI or the ASDAS, or acute-phase reactants on outcomes in patients with AS. In clinical settings, the use of BASDAI and ASDAS instruments is not uniformly adopted and other factors other than disease activity often play a role when making treatment decisions. Medical necessity for treatment escalation to a biologic or Janus Kinase (JAK) inhibitor requires that patients have high disease activity which may be defined by BASDAI or ASDAS scores if available or could be determined by a positive rheumatologists' opinion to escalate treatment based on prior failure of conventional therapies (e.g., NSAIDs) and a clinical exam which evaluates presence of ongoing bothersome symptoms, as well as laboratory exams that support ongoing inflammation.

VIII. The 2019 ACR/SAA/SPARTAN and the 2022 ASAS-EULAR guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% patients responding). No particular NSAID has been determined to be superior in efficacy or safety and guidelines don't recommend a preferred choice. Guidelines recommend that lack of response (or intolerance) to at least two different NSAIDs at maximal doses over one month, or incomplete responses to at least two different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with Tumor Necrosis Factor (TNF) inhibitors.

IX. For those patients with inadequate response despite continuous NSAID treatment, the 2019 ACR/SAA/SPARTAN panel recommends the use of TNF inhibitors as the preferred next choice due to experience and familiarity with their long-term safety and toxicity. Guidelines do not recommend any particular TNF inhibitor as the preferred choice. For those patients with continued active disease, the panel conditionally recommends a trial of a different TNF inhibitor over treatment with a non-TNF inhibitor in patients with secondary nonresponse to TNF inhibitor (those that initially responded and subsequently lost response over time). In patients that never responded to a first trial of a TNF inhibitor (primary nonresponse), trial of a different TNF inhibitor is <u>not</u> recommended and use of subsequent biologics of JAK inhibitors is preferred. Patients presenting with peripheral arthritis symptoms have additional treatment options before escalating to a biologic, which include sulfasalazine and local glucocorticoid (GC) injections.

X. In patients with intolerance, contraindications, or loss of efficacy with TNF inhibitors, the 2019 ACR/SAA/SPARTAN guidelines recommend IL-17A inhibitors next, followed by JAK inhibitors.

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 Rheumatoid Arthritis (RA), reflective of a JAK inhibitor class effect, or specific to tofacitinib (Xeljanz). Until more data becomes available, the 2022 ASAS-EULAR guidelines advise 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.

XI. According to the 2022 ASAS-EULAR and 2019 ACR/SAA/SPARTAN guidelines, treatment decisions may differ for patients presenting with EMMs. For example, for those with SpA and comorbid uveitis/iritis, adalimumab, infliximab, golimumab, and certolizumab pegol may be preferred over etanercept as this TNF inhibitor showed contradictory results. Secukinumab was shown to be unsuccessful in patients with non-infectious uveitis while rates of uveitis flares with ixekizumab have not been well-defined. For patients with comorbid inflammatory bowel disease (IBD), TNF inhibitors are preferred (except etanercept which is not effective in IBD). Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease. Increased risks of IBD exacerbation appear to also occur with ixekizumab. For psoriasis and SpA, guidelines suggest that IL-17 inhibitors may be preferred, however, no comparative data is available on psoriasis patients with axSpA. For the treatment of psoriasis and SpA, a product that is FDA approved for both indications is preferred.

XII. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend against the addition of sulfasalazine or methotrexate to biologic drugs and do not recommend these treatments for those with predominantly axial disease symptoms. This is based off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these agents may be considered for patients with ankylosing spondylitis with predominantly peripheral arthritis symptoms. Similar recommendations are made by the 2022 ASAS/EULAR guidelines.

XIII. 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.

XIV. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XV. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XVI. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. 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.
2. 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.
3. 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.
4. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor-α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. *Health Technol Assess.* 2016;20(9):1-vi. doi:10.3310/hta20090.
5. Ward MM, Deodhar A, Gensler LS, et al. 2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(10):1599-1613.
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.
10. Baraliakos X, Deodhar A, van der Heijde D, et al. Bimekizumab treatment in patients with active axial spondyloarthritis: 52-week efficacy and safety from the randomised parallel phase 3 BE MOBILE 1 and BE MOBILE 2 studies. Ann Rheum Dis. 2024;83(2):199-213. Published 2024 Jan 11. doi:10.1136/ard-2023-224803
11. Deodhar A. What is non-radiographic axial spondyloarthritis? Spondylitis Association of America. Accessed October 25, 2024. https://spondylitis.org/spondylitis-plus/what-is-non-radiographic-axial-spondyloarthritis/
12. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
13. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.

14. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
15. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Plaque Psoriasis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), secukinumab (Cosentyx), apremilast (Otezla/Otezla XR), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma), risankizumab (Skyrizi), or guselkumab (Tremfya)** may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. **Mild to moderate plaque psoriasis** when the following are met:
         i. The request is for apremilast (Otezla/Otezla XR); **AND**
         ii. Member has chronic disease (greater than 6 months), and a body surface area under 10% unless areas of the face, ears, hands, feet, genitalia are involved (moves to moderate-severe disease); **AND**
         iii. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
            a. Phototherapy (UVB or PUVA) unless it is contraindicated: **OR**
            b. Treatment with at least <u>one</u> of the following groups has been ineffective or not tolerated, unless 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., pimecrolimus cream, tacrolimus ointment)
               iii. Group 3: Topical vitamin D analogue (e.g., calcipotriene)
               iv. Group 4: Topical retinoid (i.e., tazarotene); **OR**
      2. **Moderate to severe plaque psoriasis** when the following are met:
         i. Member is being managed by, or in consultation with, a dermatologist; **AND**
         ii. Chronic disease (greater than 6 months), and at least 10% of body surface area is involved or involves areas of the face, ears, hands, feet or genitalia; **AND**
         iii. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
            a. Phototherapy (UVB or PUVA); **OR**
            b. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.)

II. **Certolizumab (Cimzia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A) above are met; **AND**
   B. Treatment with <u>two</u> of the following has been ineffective or not tolerated, or <u>all</u> are contraindicated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz

(Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], guselkumab (Tremfya), risankizumab (Skyrizi), and apremilast (Otezla/Otezla XR)

III. **Brodalumab (Siliq), ixekizumab (Taltz), bimekizumab (Bimzelx), non-preferred ustekinumab biosimilars, or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A) above are met; **AND**

B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), certolizumab (Cimzia), apremilast (Otezla/Otezla XR), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], guselkumab (Tremfya), and risankizumab (Skyrizi) have been ineffective, contraindicated, or not tolerated; **AND**

1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated; **OR**
2. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars [ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)] have been ineffective, contraindicated, or not tolerated.

IV. **Brand Humira or brand Stelara** may be considered medically necessary when the following criteria below are met:

A. Criteria I(A) above are met; **AND**

B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
   i. If the request is for **brand Humira**, treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, contraindicated, or not tolerated ; **OR**
   ii. If the request is for **brand Stelara**, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, not tolerated, or are contraindicated; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or

more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), certolizumab (Cimzia), secukinumab (Cosentyx), apremilast (Otezla/Otezla XR), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], guselkumab (Tremfya), and risankizumab (Skyrizi)

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/Otezla XR, Xeljanz, Olumiant, Rinvoq, etc.); **AND**
    A. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. 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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
            ii. If the request is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)]; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **AND**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            i. Was life-threatening; **OR**

ii. Required hospitalization; **OR**
iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved in the treatment of moderate to severe plaque psoriasis in adult patients. Otezla/Otezla XR, a small-molecule therapy, is the only specialty agent approved for mild psoriasis, making it approved for psoriasis at any severity. As of July 2024, only apremilast (Otezla/Otezla XR), etanercept (Enbrel), ixekizumab (Taltz), ustekinumab (Stelara), and secukinumab (Cosentyx) have been studied and approved for use in pediatric patients. Etanercept (Enbrel) is indicated in patients at least four years of age; apremilast (Otezla/Otezla XR), ixekizumab (Taltz), ustekinumab (Stelara), and secukinumab (Cosentyx) are indicated in patients at least six years of age.

III. Adalimumab (Humira), apremilast (Otezla/Otezla XR), brodalumab (Siliq), certolizumab (Cimzia), etanercept (Enbrel), ixekizumab (Taltz), guselkumab (Tremfya), risankizumab (Skyrizi), secukinumab (Cosentyx), and ustekinumab (Stelara) statistically significantly improves PASI by at least 90% in patients with moderate to severe plaque psoriasis compared to placebo.

IV. As of March 2021, there are four head-to-head trials that studied both induction and maintenance treatment, 14 head-to-head induction trials, and seven head-to-head maintenance trials published. Although head-to-head comparisons have shown statistical advantages for one product over another, the clinical meaningfulness of these differences remain unknown, and all products offer improvements in relevant outcomes with comparable safety profile.

- Induction and maintenance:
  i. The following agents statistically and significantly improve PASI by at least 90% compared to ustekinumab (Stelara): brodalumab (Siliq) with low certainty evidence; bimekizumab (Bimzelx), risankizumab (Skyrizi), and secukinumab (Cosentyx) with moderate certainty.
- Induction:
  i. The following agents statistically significantly improve PASI by at least 90% compared to adalimumab (Humira) with moderate certainty: guselkumab (Tremfya) and risankizumab (Skyrizi).

ii. The following agents statistically and significantly improve PASI by at least 90% compared to etanercept (Enbrel) with moderate certainty: certolizumab (Cimzia), ixekizumab (Taltz), and ustekinumab (Stelara).
iii. Ixekizumab (Taltz) statistically significantly improves PASI by at least 90% compared to ustekinumab (Stelara) with moderate certainty.
iv. There is insufficient evidence to suggest that etanercept (Enbrel) is statistically inferior to apremilast (Otezla/Otezla XR).

- Maintenance:
  i. Guselkumab (Tremfya) statistically significantly improves PASI by at least 90% compared to adalimumab (Humira) and secukinumab (Cosentyx) with moderate certainty.
  ii. Secukinumab (Cosentyx) statistically significantly improves PASI by at least 90% compared to etanercept (Enbrel) with low certainty.

V. **2019 American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) guidelines of care for the management and treatment of psoriasis with biologics:**

- "Majority of patients with mild to moderate disease (<10% BSA) are capable of adequately controlling disease solely with topical mediations or phototherapy."
- Guidelines define moderate psoriasis by 3 – 10% of the total body surface area involved and severe psoriasis is defined as ≥10% BSA involvement; however, psoriasis can be considered severe irrespective of BSA when it occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus.
- Biologics may be considered as monotherapy or in combination with other topical or systemic agents in patients with moderate to severe plaque psoriasis.
- Guidelines provide a Grade A recommendation for use of adalimumab (Humira), apremilast (Otezla/Otezla XR), brodalumab (Siliq), etanercept (Enbrel), guselkumab (Tremfya), ixekizumab (Taltz), secukinumab (Cosentyx), and ustekinumab (Stelara) and a Grade B recommendation for risankizumab (Skyrizi) as a monotherapy treatment option in adult patients with moderate to severe plaque psoriasis. Guidelines were published in 2019 and precede the FDA-approval of risankizumab; however, phase II and phase III risankizumab (Skyrizi) trials were available and included during guideline development.
- Guidelines have not provided recommendations for certolizumab (Cimzia) and bimekizumab (Bimzelx).
- Guidelines do not point to a specific agent or class when initiating treatment with a biologic. Primary failure is defined as those who are nonresponsive to initial biologic treatment whereas secondary failure represents those who initially respond but lose efficacy over time. Guidelines suggest primary failure to one agent does not preclude successful response to another agent under the same class; however, this may foretell reduced efficacy.
- Guidelines do not provide recommendations for switching therapies.
- Guidelines provide a Grade C recommendation indicating use for adalimumab (Humira), etanercept (Enbrel), or ustekinumab (Stelara) may be combined with apremilast (Otezla/Otezla XR) to augment efficacy for the treatment of moderate to severe plaque psoriasis in adults when clinically indicated. This recommendation comes from consensus guidelines, opinion, case studies, or disease-oriented evidence. There is lack of patient-oriented evidence to support combination use with other biologics or other non-biologic specialty medications used to treat plaque psoriasis. Therefore, coverage for combination

use with other biologics or other non-biologic specialty medications remains experimental and investigational.

- Mild to moderate psoriasis: Guidelines state that because psoriasis generally recurs after discontinuation of topical corticosteroid treatment, it is important to consider using steroid sparing agents that have been developed to supplement and reduce over-reliance on topical corticosteroids as monotherapy, decreasing the risk of corticosteroid adverse effects. Agents such as vitamin D analogues (Grade A recommendation), topical retinoids (Grade B recommendation), and calcineurin inhibitors (Grade B recommendation) can be used as a maintenance treatment.
- As of January 2022, the guidelines have not been updated to place apremilast (Otezla/Otezla XR) into a routine place of care in the treatment of mild to moderate psoriasis over the current guidelines of phototherapy, topical treatments, or a systemic DMARD.

VI. Coverage for the above agents in the setting of palmoplantar psoriasis (defined as psoriasis of the palms or soles presenting with hyperkeratotic, erythematous, plaques and fissures) may be appropriate when criteria for moderate-severe plaque psoriasis are met. Medical necessity for the treatment of guttate psoriasis and/or palmoplantar ***pustulosis*** are reviewed in the experimental and investigational section of this policy.

VII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

VIII. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

IX. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment

failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. Adalimumab (Humira) [Prescribing Information]. North Chicago, IL; AbbVie. Updated March 2020.
2. Apremilast (Otezla/Otezla XR) [Prescribing Information]. Thousand Oaks, CA; Amgen. Updated December 2021.
3. Brodalumab (Siliq) [Prescribing Information]. Bridgewater, NJ; Bausch Health. Updated April 2020.
4. Certolizumab pegol (Cimzia) [Prescribing Information]. Smyrna, GA; UCB. Updated September 2019.
5. Etanercept (Enbrel) [Prescribing Information]. Thousand Oaks, CA; Amgen. Updated August 2020.
6. Ixekizumab (Taltz) [Prescribing Information]. Indianapolis, IN; Eli Lilly. Updated May 2020.
7. Guselkumab (Tremfya) [Prescribing Information]. Horsham, PA; Janssen. Updated July 2020.
8. Risankizumab (Skyrizi) [Prescribing Information]. North Chicago, IL; AbbVie. Updated March 2020.
9. Secukinumab (Cosentyx) [Prescribing Information]. East Hanover, NJ; Novartis. Updated June 2020.
10. Ustekinumab (Stelara) [Prescribing Information]. Horsham, PA; Janssen. Updated July 2020.
11. Bimekizumab (Bimzelx) [Prescribing Information]. Smyrna, GA. UCB, Inc. October 2023.
12. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2019;80(4):1029-1072.
13. 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. J Amer Academy of Dermol 2020;82:1445-86.
14. Sbidian E, Chaimani A, Afach Sivem et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev* 2020;1(1):1-602.
15. Singh S, Singh S, Thangaswamy A et al. Efficacy and safety of Risankizumab in moderate to severe psoriasis: A systematic review and meta-analysis*. Dermatol Ther* 2020;e14487.
16. Sawyer LM, Cornic L, Levin LA et al. Long-term efficacy of novel therapies in moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis of PASI response. *J Eur Acad Dermatol Venereol* 2019;33(2):355-366.
17. Lebwohl M, Blauvelt A, Paul C et al. Certolizumab pegol for the treatment of chronic plaque psoriasis: Results through 48 weeks of a phase 3, multicenter, randomized, double-blind, etanercept- and placebo-controlled study (CIMPACT). *Acad Dermatol* 2018;79(2):266-276.
18. Reich K, Armstrong AW, Langley RG et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet* 2019;394(10201):831-839.
19. UpToDate, Inc. Psoriasis: Epidemiology, clinical manifestations, and diagnosis. UpToDate [database online]. Waltham, MA. Last updated December 30, 2019. Available at: http://www.uptodate.com/home/index.html.
20. Stein Gold L, Papp K, Pariser D, et al. Efficacy and safety of apremilast in patients with mild-to-moderate plaque psoriasis: Results of a phase 3, multicenter, randomized, double-blind, placebo-controlled trial. J Am Acad Dermatol. 2022 Jan;86(1):77-85. doi: 10.1016/j.jaad.2021.07.040. Epub 2021 Jul 31. PMID: 34343599.
21. Fiorillo L, Becker E, de Lucas R, et al. Efficacy and safety of apremilast in pediatric patients with moderate-to-severe plaque psoriasis: 16-week results from SPROUT, a randomized controlled trial. *J Am Acad Dermatol*. 2024;90(6):1232-1239. doi:10.1016/j.jaad.2023.11.068
22. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
23. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
24. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
25. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Crohn's Disease

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), guselkumab (Tremfya), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma), or risankizumab (Skyrizi)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   B. Diagnosis of **moderate to severe Crohn's disease**; **AND**
   C. 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)

II. **Vedolizumab SC (Entyvio) or certolizumab (Cimzia)** may be considered medically necessary when the following criteria are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with two of the following have been ineffective, contraindicated, or all are not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], guselkumab (Tremfya), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], risankizumab (Skyrizi), or upadacitinib (Rinvoq); **OR**
      1. Member has achieved remission of disease using Entyvio IV and is continuing therapy with the SC formulation.

III. **Mirikizumab (Omvoh), non-preferred ustekinumab biosimilars, or non-preferred adalimumab biosimilars** 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)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], certolizumab (Cimzia), guselkumab (Tremfya), risankizumab (Skyrizi), vedolizumab SC (Entyvio), and upadacitinib (Rinvoq) have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated; **OR**

IV. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars (ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma) have been ineffective, contraindicated, or not tolerated. **Infliximab-dyyb (Zymfentra)** is considered not medically necessary when used for all conditions, including but not limited to, maintenance of remission in Crohn's disease in place of intravenous (IV) formulation.
   A. Infliximab-dyyb (Zymfentra) is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in Crohn's disease. Intravenous (IV) formulation is clinically comparable in efficacy and safety to the subcutaneous (SC) formulation and is the preferred product which can be accessed via the

medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

V. **Brand Humira or brand Stelara** 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 brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
      1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. If the request is for brand Humira, treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
         ii. If the request is for brand Stelara, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, contraindicated, or not tolerated; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications, and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **AND**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma)], certolizumab (Cimzia), guselkumab (Tremfya), risankizumab (Skyrizi), vedolizumab SC (Entyvio), and upadacitinib (Rinvoq)

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/Otezla XR, Xeljanz, Olumiant, Infliximab, etc.); **AND**

A. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

B. 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**

1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    ii. If the request is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)]; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications, and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are 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), guselkumab (Tremfya), ustekinumab (Stelara), risankizumab (Skyrizi), infliximab-dyyb (Zymfentra), mirikizumab (Omvoh), and vedolizumab SC (Entyvio) are FDA-approved in adults only, while adalimumab (Humira) is approved in patients six years of age and older.

III. 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.

IV. 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 the occurrence of disease complications, such as stricture and fistula.

Moderate to severe CD

V. 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.

VI. The symptoms of CD do not correlate well with the 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.

VII. 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.

VIII. 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).

IX. 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 the use of thiopurines over no treatment for the maintenance of remission (conditional recommendation, low level of evidence).

X. 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.

XI. Adalimumab (Humira), ustekinumab (Stelara), certolizumab (Cimzia), infliximab (e.g., Remicade, Inflectra), vedolizumab (Entyvio), natalizumab (Tysabri), guselkumab (Tremfya), risankizumab (Skyrizi), mirikizumab (Omvoh), and infliximab-dyyb (Zymfentra) 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.

XII. The timing of introduction of biologic agents is a matter of debate and more studies are needed to assess a 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

XIII. Patients who are considered to have severe/fulminant disease are those with persistent symptoms despite the 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.

XIV. 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 a case-by-case basis.

Pediatric CD

XV. Children and adolescents with CD often present with a more complicated disease course compared to adult patients. Additionally, the potential impact of CD on growth, pubertal, and

emotional development warrants a specific management strategy. The goals of therapy in pediatric CD are to relieve symptoms, achieve remission, optimize growth, and improve quality of life while minimizing drug toxicity.

XVI. Oral corticosteroids are recommended for inducing remission in children with moderate to severe active luminal CD. Corticosteroids should not be used as maintenance therapy. Thiopurines (azathioprine or 6-mercaptopurine) and methotrexate are recommended options for maintenance of steroid free remission in children at risk for poor disease outcomes. Methotrexate can be used as primary maintenance therapy or in thiopurine failure.

XVII. Anti-TNF-alpha therapy is recommended for inducing and maintaining remission in children with chronically active luminal CD despite prior optimized immunomodulator therapy or with active steroid-refractory disease. Anti-TNF-alpha therapy is recommended as primary induction and maintenance therapy for children with active perianal and fistulizing disease and can be considered for selected children with high risk for poor outcomes. According to ECCO/ESPGHAN clinical guidelines on the management of pediatric CD, early use of immunomodulators and biologics warrants selection of ideal candidates who are at high risk for developing severe disease and depends on predictive factors. Predictive factors are largely the same as the ones for adults but further include the presence of marked growth retardation (>-2.5 height Z scores) and severe osteoporosis.

XVIII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XIX. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XX. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment

failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

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. Infliximab (Zymfentra) [Prescribing Information] Jersey City, NJ; Celltrion USA Inc., October 2023
6. Vedolizumab (Entyvio) [Prescribing Information]. Cambridge, MA, Takeda., April 2024.
7. Mirikizumab (Omvoh) [Prescribing information]. Indianapolis, IN. January 2025.
8. 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
9. 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
10. 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
11. 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.
12. 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
13. 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.
14. 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
15. 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
16. Vermeire S, D'Haens G, Baert F, et al. Efficacy and Safety of Subcutaneous Vedolizumab in Patients With Moderately to Severely Active Crohn's Disease: Results From the VISIBLE 2 Randomised Trial. J Crohns Colitis. 2022;16(1):27-38. doi:10.1093/ecco-jcc/jjab133
17. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
18. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
19. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
20. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Ulcerative Colitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), guselkumab (Tremfya), ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma), or risankizumab (Skyrizi)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   B. Diagnosis of **moderate to severe ulcerative colitis; AND**
   C. 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

II. **Vedolizumab SC (Entyvio)** may be considered medically necessary when the following criteria are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with two of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], guselkumab (Tremfya), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], risankizumab (Skyrizi), tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq); **OR**
      1. Member has achieved remission of disease using Entyvio IV and is continuing therapy with the SC formulation.

III. **Golimumab (Simponi), ozanimod (Zeposia), mirikizumab (Omvoh), etrasimod (Velsipity), non-preferred ustekinumab biosimilars, or non-preferred adalimumab biosimilars** 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)], guselkumab (Tremfya), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], risankizumab (Skyrizi), vedolizumab SC (Entyvio), tofacitinib (Xeljanz/Xeljanz XR), and upadacitinib (Rinvoq) have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated; **OR**
      2. If the request is for non-preferred ustekinumab biosimilars, at least three preferred ustekinumab biosimilars [ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)] have been ineffective, contraindicated, or not tolerated.

IV. **Infliximab-dyyb (Zymfentra)** is considered not medically necessary when used for all conditions, including but not limited to, maintenance of remission in ulcerative colitis in place of intravenous (IV) formulations.
   A. Infliximab-dyyb (Zymfentra) is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis. Intravenous (IV) formulations are clinically comparable in efficacy and safety to the SC formulations and are the preferred products which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

V. **Brand Humira or brand Stelara** 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 brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. If the request is for brand Humira, treatment with adalimumab-bwwd (Hadlima) AND adalimumab-adaz (Adalimumab-ADAZ) have been ineffective, not tolerated, or are contraindicated; **OR**
        ii. If the request is for brand Stelara, treatment with ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), AND ustekinumab-stba (Steqeyma) have been ineffective, contraindicated, or not tolerated; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **AND**
D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], guselkumab (Tremfya), risankizumab (Skyrizi), vedolizumab SC (Entyvio), tofacitinib (Xeljanz/Xeljanz XR), and upadacitinib (Rinvoq)

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, Cimzia, etc.); **AND**
    A. If the request is for **Brand Humira or Brand Stelara**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. 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**

1. The member experienced a documented sever intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
    i. If the request is for brand Humira, at least two adalimumab biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima)and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    ii. If the reqeuest is for brand Stelara, at least three ustekinumab biosimilars have been tried [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), and ustekinumab-stba (Steqeyma)]; **OR**
2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are FDA approved in the treatment of moderate to severe ulcerative colitis (UC) in adult patients. 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.

III. Adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi), 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), golimumab

(Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi) is incremental or better when evaluated against placebo.

IV. Comparative efficacy and safety data are only available for vedolizumab (Entyvio) and adalimumab (Humira) at this time. There is low certainty that vedolizumab (Entyvio) has a comparable or better net health benefit compared to adalimumab (Humira) for induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe UC. Vedolizumab (Entyvio) was found to be statistically superior with respect to certain efficacy outcomes; however, efficacy and safety is regarded as clinically comparable between the two agents.

V. The safety and efficacy of adalimumab (Humira) for the treatment of moderate to severe ulcerative colitis in pediatric patients aged five years and older was evaluated in one phase 3, double-blind, randomized, historical placebo controlled clinical trial (ENVISION-1). The trial included 93 patients, the majority of which were previously treated with corticosteroids and immunosuppressants at baseline and majority of patients (84%) were anti-TNF therapy naïve. Due to challenges with enrollment in the placebo arm, the trial underwent protocol amendments and was partially open label. The clinical trial studied two adalimumab (Humira) doses: 0.6 mg/kg every week (high dose) and 0.6 mg/kg every other week (standard dose). The two primary efficacy outcomes, Partial Mayo Score (PMS) and Full Mayo Score (FMS), were statistically significant against historical placebo in the high dose adalimumab (Humira) arm only, with 60% [95% CI: 44%-74%] of patients achieving PMS during induction and 45% [95% CI: 27%-64%] of patients achieving FMS during maintenance. During induction and maintenance phases, 22% and 37% of patients, respectively, experienced infections. There were 8% of patients which experienced serious infections, and 11% and 14% of patients experienced serious adverse events in the induction and maintenance phases, respectively.

VI. 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, the 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.

VII. 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.

VIII. 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.

IX. In September 2024, guselkumab (Tremfya) was approved for adults with moderate to severe UC. For the treatment of UC, guselkumab (Tremfya) is administered as a 200 mg intravenous (IV) induction dose at Weeks 0, 4, and 8 followed by a maintenance dose of 100 mg subcutaneously (SC) at Week 16 and every 8 weeks thereafter, or 200 mg SC at Week 12 and every 4 weeks thereafter. This approval was based on the ongoing QUASAR trial, which included a Phase 2b dose-ranging induction study of IV guselkumab (Tremfya), a confirmatory Phase 3 induction study, and a Phase 3 maintenance study. All participants had failed conventional therapies (thiopurines/corticosteroids) and 50% had failed two or more advanced therapies (i.e., TNF inhibitors, vedolizumab, tofacitinib). The primary endpoint of the Phase 2B IV portion of the trial was clinical remission measured at week 12, with the primary endpoint of the maintenance Phase 3 portion, sustained remission. A significantly greater proportion of patients in the guselkumab (Tremfya) group achieved clinical remission compared with those in the placebo group (22.6% vs 7.9%, respectively; adjusted treatment difference, 14.9%; $P<0.001$) at week 12; and, at week 44, 45.2% of patients on guselkumab (Tremfya) 100mg every 8 weeks, 50.0% on 200mg every 4 weeks, and 18.0% on placebo sustained remission. Adjusted treatment difference of 25.2%, *p<0.001* for 100mg and 29.5%, *p<0.001* for 200mg versus placebo. The largest number of ADE were COVID-19 infections and arthralgias (6.1% guselkumab [Tremfya] vs 6.8% placebo).

X. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. Adalimumab (Humira) [Prescribing Information]. North Chicago, IL; AbbVie. Updated December 2020.
2. Ustekinumab (Stelara) [Prescribing Information]. Horsham, PA; Janssen. Updated December 2020.
3. Golimumab (Simponi) [Prescribing Information]. Raritan, NJ; Janssen Biotech, Inc. Updated September 2019.
4. Infliximab (Remicade) [Prescribing Information]. Raritan, NJ; Janssen Biotech, Inc. Updated May 2020.
5. Vedolizumab (Entyvio) [Prescribing Information]. Cambridge, MA; Takeda Inc., Updated September 2023.
6. Ozanimod (Zeposia) [Prescribing Information]. New York, NY; Bristol Myers Squibb Inc., Updated May 2021.
7. Tofacitinib (Xeljanz) [Prescribing Information]. New York, NY; Pfizer Inc., Updated September 2020.
8. Mirikizumab (Omvoh) [Prescribing Information]. Indianapolis, IN; Eli Lilly, Inc. Updated November 2023.
9. Etrasimod (Velsipity) [Prescribing Information]. New York, NY; Pfizer Inc., October 2023.
10. Infliximab (Zymfentra) [Prescribing Information]. Jersey City, NJ; Celltrion USA Inc., October 2023.
11. Risankizumab (Skyrizi) [Prescribing Information]. North Chicago, IL; AbbVie. Updated June 2024.
12. 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.
13. 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
14. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1215-1226. doi:10.1056/NEJMoa1905725. PMID: 31553834.
15. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1201-1214. doi: 10.1056/NEJMoa1900750. PMID: 31553833.
16. 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.
17. 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.
18. 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.
19. Zeposia (ozanimod) Clinical Summary: TRUENORTH phase 3 trial for Ulcerative Colitis. Bristol Myers Squibb. December 2020.
20. 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.

21. Tremfya (guselkumab) [Prescribing Information] Horsham, PA; Janssen Biotech, Inc., Updated September 2024.
22. The Efficacy and Safety of Guselkumab Induction Therapy in Patients With Moderately to Severely Active Ulcerative Colitis: Results From the Phase 3 QUASAR Induction Study. *Gastroenterol Hepatol (N Y)*. 2023;19(7 Suppl 3):9-10.
23. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
24. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
25. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
26. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Behcet's Disease (i.e., Behcet Syndrome)

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), or apremilast (Otezla/Otezla XR)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a specialist that is treatment this condition (e.g., rheumatologist, dermatologist, ophthalmologist, etc.); **AND**
      1. A diagnosis of recurrent **Behcet's Disease manifesting as oral ulcers of the mouth**; **AND**
         i. One of the following have been ineffective, not tolerated, or all are contraindicated:
            a. Topical corticosteroids (e.g., triamcinolone) OR sucralfate mouthwash; **OR**
            b. Systemic therapy (e.g., colchicine, thalidomide, prednisone, benzathine penicillin); **OR**
      2. A diagnosis of **Behcet's disease manifesting as uveitis**; **AND**
         i. All of the following have been ineffective, not tolerated, or are contraindicated;
            a. Oral corticosteroids; **AND**
            b. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.)

II. **Non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], apremilast (Otezla/Otezla XR), and etanercept (Enbrel) have been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A) above are met; **AND**

B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **AND**
D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: apremilast (Otezla/Otezla XR) and etanercept (Enbrel)

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 of disease symptoms (reduction in inflammation, and/or lesions, reduction in amount of oral glucocorticoids needed, reduction in number of flares, etc.); **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Behcet's Disease or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, Rinvoq, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. 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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**

i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**

2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage(*as confirmed by a health plan pharmacist*); **OR**
3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
   i. Was life-threatening; **OR**
   ii. Required hospitalization; **OR**
   iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Adalimumab (Humira) and Etanercept (Enbrel) are not FDA-approved for the treatment of any manifestation of Behcet's Disease; however, several studies are available to support the use of these agents for various manifestations of the disease. Notably, mouth ulcers and ophthalmic complications. Examples are provided below.
   - Trial of etanercept in Behcet's Disease, double blind, placebo-controlled trial: 40 patients with mucocutaneous disease were enrolled in a trial evaluating etancercept compared to placebo. Results indicated efficacy of etanercept on oral ulcers, nodular lesions, papulopustular lesions, and had an increased probability of being ulcer and nodular lesion free compared to the placebo group. Although a small trial, the rarity of Behcet's Disease shall be taken into account.
   - A multicenter study of refractory Behcet's Disease treated with and-TNF alpha treatments was conducted: The trial included infliximab and adalimumab. These therapies resulted in an overall 90.4% response rate for all clinical manifestations, and specifically an 88% response rate for mucocutaneous manifestations and 96.3% for severe and/or refractory ocular disease. The incidence of flares was reduced during anti-TNF alpha treatment.

- An analysis of published data in 369 patients using anti-TNF alpha agents for Behcet's Disease: This included peer-reviewed articles on Medline/PubMed and evaluated patients that were uncontrolled with or intolerant to other immunosuppressives. A rate of 90% clinical response was seen for the mucocutaneous manifestations of Behcet's disease, and a rate of 89% for ocular disease.

III. Behcet's Disease may manifest in many forms; however, it is commonly managed by rheumatology specialists; however, there may be instances when other inflammatory specialists may be managing and prescribing.

IV. Corticosteroids and oral DMARDS (typically azathioprine) have been mainstays of Behcet's Disease, with oral DMARDS having a particular role in ophthalmic manifestations.

V. For oral manifestations first line treatment is triamcinolone acetonide cream 0.1% in orabase, applied three to four times daily. High potency topical steroids may also be employed. Topical sucralfate may also be used with or as an alternative to topical corticosteroids. A strength of 1 gram/5 mL four times daily as a mouthwash is recommended to reduce pain, frequency, and healing time.

VI. In the latest 2018 EULAR recommendations in the treatment of Behcet's Disease, colchicine is used as the first-line treatment of mucocutaneous lesions. As well as benzathine penicillin, which is often added to colchicine to increase the effectiveness. Thalidomide is often helpful but should be used in caution in selected patients because of potential side effects. In acute and severe attacks of mucocutaneous lesions, oral corticosteroids can be used as an effective treatment. Additional other oral DMARDS (such as azathioprine) may be useful but are supported with less clinical evidence and are more case by case in nature of providing disease control or management.

VII. Apremilast (Otezla/Otezla XR) was evaluated for Behcet's Disease in the following trial: Efficacy of apremilast for oral ulcers associated with active Behcet's Syndrome in a Phase III study. This indication was FDA-approved for treatment of oral ulcers of the mouth associated with Behcet's Disease in July 2019. A total of 207 patients were randomized to apremilast or placebo, and favorable treatment effect was noted. Although apremilast is an FDA-approved medication for Behcet's Disease, anti-TNF alpha therapies have equal or greater safety and efficacy data to support their use in this condition. Guidelines and key opinion leaders have consensus in regard to use of anti-TNF alpha therapies prior to use of apremilast; however, due to limited evidence of using one anti-TNF alpha agent after failure of another, trial of more than one agent is not required.

VIII. Standard dosing for adalimumab (Humira) is 40 mg every other week, and standard dosing for Etanercept (Enbrel) is 50 mg per week, either 25 mg twice weekly or 50 mg once weekly.

IX. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

X. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a

rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XI. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. Mahr A., Takeno M., Kim DY. Efficacy of apremilast for oral ulcers associated with active Behcet's Syndrome in a phase III study: a prespecified analysis by baseline patient demographics and disease characteristics. ARHP Annual Meeting. 2018; abstract 1791.
2. Yazici H, Pazarli H, Barnes CG, et al. A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med. 1990;322(5):281-5.
3. Arida A, Fragiadaki K, Giavri E, Sfikakis PP. Anti-TNF agents for Behçet's disease: analysis of published data on 369 patients. Semin Arthritis Rheum. 2011;41(1):61-70.
4. Vallet H, Riviere S, Sanna A, et al. Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: Multicenter study of 124 patients. J Autoimmun. 2015;62:67-74.
5. Melikoglu M, Fresko I, Mat C, et al. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. J Rheumatol. 2005;32(1):98-105.
6. Alpsoy, Erkan, Leccese Pietro, et al. Treatment of Behcet's Disease: An Algorithmic Multidisciplinary Approach. *Front. Med*., April 2021
7. Hatemi G, Christensen R, Bang D, et al2018 update of the EULAR recommendations for the management of Behçet's syndromeAnnals of the Rheumatic Diseases 2018;77:808-818. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
8. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
9. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
10. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Hidradenitis Suppurativa

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a dermatologist; **AND**
   B. A diagnosis of **hidradenitis suppurativa** when the following are met:
      1. Presence of inflammatory nodules and/or abscesses; **AND**
      2. Hurley Stage III (severe) disease; **OR**
      3. Hurley Stage II (moderate) disease with:
         i. Treatment with at least one oral antibiotic (i.e., doxycycline, minocycline, tetracycline, clindamycin/rifampin, etc.) has been ineffective, contraindicated, or not tolerated

II. **Bimekizumab (Bimzelx) or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and secukinumab (Cosentyx) has been ineffective, contraindicated, or not tolerated; **AND**
      1. If the request is for non-preferred adalimumab biosimilars, at least two preferred adalimumab biosimilars [adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)] have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
      1. The member experienced a documented sever intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
      2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
      3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: secukinumab (Cosentyx)

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 abscess and inflammatory nodule count, decrease in frequency of inflammatory lesions, etc.); **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat hidradenitis suppurativa or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. 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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering

competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, inflammatory disease affecting sweat glands characterized by recurrent, painful lesions that typically develop in intertriginous areas such as the axillae, groin, vulva, or gluteal cleft/anal region. Lesions usually start small and, over weeks to months, form into nodules, abscesses, or tunnels that can lead to scarring and fistulas overtime. The disease is classified in 3 clinical stages which help guide treatment: Hurley stage I (least severe), Hurley stage II (moderate severity), and Hurley stage III (most severe).

III. Adalimumab (Humira) is FDA-approved in patients in 12 years or older with moderate to severe HS supported by results of the PIONEER I and II RCTs.

IV. In the PIONEER studies, patients were only included if they had a diagnosis of Hurley Stage II or Hurley Stage III disease, had at least three inflammatory nodules/abscesses present at baseline, and had previously had an inadequate response to at least a 3-month trial of oral antibiotics. Adalimumab met the primary end point at week 12, where the Hidradenitis Suppurativa Clinical Response (HiSCR) primary efficacy endpoint (≥50 percent reduction in the total abscess and inflammatory nodule count with no increase in the abscess or draining sinus count) was achieved with adalimumab 40mg once weekly compared to the placebo groups. A three-year, open-label, extension study that followed the PIONEER trials suggests long-term efficacy and safety of adalimumab. The OLE study found a sustained rate of response (achievement of HiSCR) over time among patients who received 40 mg of adalimumab once weekly for at least 60 weeks. No new safety concerns were raised.

V. While oral antibiotics are frequently employed in moderate to severe disease as noted above, the data for these agents primarily stems from studies in patients with Hurley Stage I and II disease. Although the combination of clindamycin/rifampin has demonstrated improvement in terms of partial or total remission, only one small study with 10 patients has examined the use in Hurley Stage III patients. Nearly 50% of patients in the PIONEER I and II studies of adalimumab had Hurley Stage III disease, and the randomized, controlled nature of the study provides greater assurance of efficacy for this more severe population than prior studies of oral antibiotics.

VI. Two phase 3, multicenter, double-blind, randomized, placebo-controlled trials (SUNSHINE and SUNRISE) evaluated the efficacy and safety of secukinumab (Cosentyx) in patients aged 18 years or older with a diagnosis of moderate to severe HS, defined as a total of five or more inflammatory lesions affecting two or more distinct anatomical areas. In both trials, this correlated to over 90 percent of participants having a diagnosis of Hurley Stage II or Hurley Stage III. Patients were randomized to secukinumab 300mg subQ every 2 weeks, every 4 weeks, or placebo. The primary endpoint evaluated the proportion of patients with a hidradenitis suppurative clinical response (HiSCR), defined as a decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or in the number of draining fistulae compared with baseline at week 16. Key secondary endpoints include change in abscess and inflammatory nodule count, number of flares, and reduction in skin pain at week 16.

- The primary endpoint was met in the SUNRISE trial, where 42% of participants on secukinumab every 2 weeks and 46% of those on secukinumab every 4 weeks achieved a clinically meaningful response in HiSCR, compared to 31% on placebo ($p<0.01$). In the SUNSHINE trial, the primary endpoint was not met in the secukinumab every 4 weeks, but secukinumab every 2 weeks achieved statistical and clinically significant change in

HiSCR (p=0.007). Based on the results of the SUNSHINE trial, secukinumab every 2 weeks may be preferred over every 4 weeks dosing, especially in regard to the primary endpoint.

- For the pooled secondary endpoints, only the SUNSHINE trial showed significantly fewer patients having flares in the secukinumab every 2 weeks group than in the placebo group during the first 16 weeks, while the SUNRISE trial showed significantly improved abscess and nodule count at week 16 in secukinumab every 4 weeks compared to placebo and statistically significant differences in the proportion of patients with flares between the secukinumab every 4 weeks group and the placebo group during the first 16 weeks. Both trials did show secukinumab improved patients' health-related quality of life (HRQoL) up to 52 weeks and many patients that did achieve a HiSCR at week 16 maintained their response at week 52.
- No new safety concerns were raised in either trial.

VII. Two Phase 3, multicenter, double-blind, randomized, placebo-controlled trials (BE HEARD I and BE HEARD II) evaluated the efficacy and safety of bimekizumab (Bimzelx) in patients aged 18 years or older with a diagnosis of moderate to severe HS, defined as a total of five or more inflammatory lesions affecting two or more distinct anatomical areas. In both trials, participants had HS severity corresponding to Hurley Stage II or Hurley Stage III. The primary endpoint evaluated the proportion of patients with a hidradenitis suppurative clinical response (HiSCR50), defined as a decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or in the number of draining fistulae compared with baseline at week 16. Key secondary endpoints included attainment of HiSCR75 response, number of flares, change in the Dermatology Life Quality Index (DLQI) and reduction in skin pain at week 16.

- The primary endpoint was met in both trials at week 16, where 48% (BE HEARD I) and 52% (BE HEARD II) of participants on bimekizumab (Bimzelx) every 2 weeks achieved a clinically meaningful response in HiSCR50, compared to 29% (BE HEARD I) and 32% (BE HEARD II) on placebo ($p<0.006$; $p<0.003$, respectively).
- For secondary endpoints, HiSCR75 was statistically significant in both trials for the FDA approved dose. Incidence of flares was reported only in the BE HEARD II trial which did not meet statistical significance and was numerically higher in the bimekizumab (Bimzlex) arm than in placebo (29% vs 28%, p=0.87). HRQoL improvements were reported to be statistically and clinically meaningful at week 16 and skin pain response was numerically better with bimekizumab (Bimzelx) compared to placebo (32% vs 15%, p=0.41). Both trials showed that response was either higher or maintained at week 52.
- No new safety concerns were raised in either trial.

VIII. The Unites States and Canadian Hidradenitis Suppurativa Foundation 2019 guidelines provide recommendations for the treatment of HS. For mild-to-moderate HS, systemic antibiotics including tetracyclines are recommended as monotherapy and clindamycin and rifampin in combination is recommended in the second-line setting. For severe disease, clindamycin and rifampin may be used as a first line or adjunct treatment. For moderate-to-severe disease, moxifloxacin, metronidazole, and rifampin in combination are recommended as second- or third-line treatment. This recommendation is based on moderate-quality evidence from RCTs and one systemic review of retrospective and prospective studies. In moderate-to-severe disease when systemic antibiotics are ineffective or insufficient, the guidelines recommend the use of biologics, with a strong recommendation for adalimumab based on high quality evidence. Limited evidence is available for infliximab, anakinra, and ustekinumab with limitations including considerable variability and validity of end points, lack of dose ranging studies, and short follow-

up periods. As of June 2023, the guidelines have not been updated with regard to place in therapy for secukinumab.

IX. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

X. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XI. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. Kimball AB, Okun MM, Williams DA, et al. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. *N Engl J Med*. 2016;375(5):422-434.
2. Zouboulis CC, Okun MM, Prens EP, et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *J Am Acad Dermatol*. 2019;80(1):60-69.e2. doi:10.1016/j.jaad.2018.05.040
3. Ingram JR, Collier F, Brown D, et al. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *Br J Dermatol.* 2019;180(5):1009-1017.
4. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management. *J Am Acad Dermatol*. 2019;81(1):91-101. doi:10.1016/j.jaad.2019.02.068
5. UpToDate, Inc. Hidradenitis suppurativa: management. UpToDate [database online]. Waltham, MA. Last updated June 30, 2022. Available at: http://www.uptodate.com/home/index.html.

6. Gulliver W, Zouboulis CC, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. *Rev Endocr Metab Disord.* 2016;17(3):343-351.
7. Kimball AB, Jemec GBE, Alavi A, et al. Secukinumab in moderate-to-severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials. *Lancet*. 2023;401(10378):747-761. doi:10.1016/S0140-6736(23)00022-3
8. Kimball AB, Jemec GBE, Sayed CJ, et al. Efficacy and safety of bimekizumab in patients with moderate-to-severe hidradenitis suppurativa (BE HEARD I and BE HEARD II): two 48-week, randomised, double-blind, placebo-controlled, multicentre phase 3 trials. Lancet. 2024;403(10443):2504-2519. doi:10.1016/S0140-6736(24)00101-6.
9. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
10. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
11. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
12. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Uveitis and Panuveitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima) or adalimumab-adaz (Adalimumab-ADAZ)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, an ophthalmologist or rheumatologist; **AND**
   B. A diagnosis of **non-infectious intermediate, posterior, or panuveitis** when the following are met:
      1. Previous treatment with at least one periocular injection, implant, topical, or systemic corticosteroid (i.e., triamcinolone, dexamethasone, prednisone, fluocinolone, difluprednate, etc.) has been ineffective, contraindicated, or not tolerated; **AND**
      2. Previous treatment with at least one non-corticosteroid systemic immunomodulatory therapy (i.e., mycophenolate mofetil, tacrolimus, cyclosporine, azathioprine, or methotrexate) has been ineffective, contraindicated, or not tolerated.

II. **Non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ) has been ineffective, contraindicated, or not tolerated.

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **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**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage

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 uveitis and panuveitis or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. 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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**

3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Adalimumab (Humira) is FDA-approved for patients at least two years of age with non-infectious intermediate, posterior, or panuveitis based off data from the VISUAL I and II phase 3 RCTs.

III. The Fundamentals of Care for Uveitis (FOCUS) guideline recommends that the noncorticosteroid systemic immunomodulatory therapy (NCIST) agents listed above may be indicated for patients who have a failure or lack of tolerance to regional or systemic corticosteroids. Prior to initiation of alternative medications such as biologic agents, guidelines recommend dose escalation to the maximum tolerated/effective dose of NCIST. It is noted that use of biologic agents is supported for adalimumab, infliximab, and interferon alpha-2a.

IV. A meta-analysis published recently in 2018 supports this statement of biologic utility in uveitis. The analysis included 3 RCTs and 20 non-RCTs that examined adalimumab use in patients with non-infectious uveitis, with reduced time to treatment failure and improvements in visual acuity demonstrated.

V. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

VI. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease

control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

VII. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10050):1183-1192.
2. Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med*. 2016;375(10):932-943.
3. Dick AD, Rosenbaum JT, Al-dhibi HA, et al. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. *Ophthalmology*. 2018;125(5):757-773.
4. Ming S, Xie K, He H, Li Y, Lei B. Efficacy and safety of adalimumab in the treatment of non-infectious uveitis: a meta-analysis and systematic review. *Drug Des Devel Ther.* 2018;12:2005-2016.
5. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
6. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
7. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
8. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Giant Cell Arteritis

Initial Evaluation

I. **Tocilizumab-aazg (Tyenne)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **giant cell arteritis** when the following are met:

1. Member is 18 years of age or older; **AND**
    i. A diagnosis of **giant cell arteritis** positively confirmed by one of the following:
        a. Temporal artery biopsy
        b. Doppler ultrasound
        c. Magnetic resonance angiography (MRA)
        d. Positron emission tomography (PET)

II. **Brand Actemra** may be considered medically necessary when the following criteria below are met:
    A. Criteria I(A)-I(B) 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 a biosimilar product; **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**
        1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **OR**
            i. Documentation of treatment with tocilizumab-aazg (Tyenne) has been ineffective, contraindicated, or not tolerated; **OR**
        2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage; **AND**

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/Otezla XR, Xeljanz, Olumiant); **AND**
    A. If the request is for **Brand Actemra**: 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 biosimilar; **AND**

B. 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**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. tocilizumab-aazg (Tyenne) has been tried; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Giant cell arteritis (GCA) is an inflammatory vascular condition that is most frequently occurring in adult patients 50 years of age or older. It manifests with fever, fatigue, headache, transient or permanent vision loss, and large vessels involved like the aorta, and major vessels in upper extremities. Large vessel involvement includes dissections, aneurysm, tenderness to palpation, or asymmetric blood pressure. This condition is associated with elevated serum ESR and CRP levels and it is often closely related to polymyalgia rhematic disease.

II. Tocilizumab (Actemra) is FDA-approved for adult patients with giant cell arteritis based off results of a phase 3 RCT. In this trial, 251 patients were randomized to subcutaneous tocilizumab plus a prednisone taper or placebo plus a prednisone taper. The primary outcome of glucocorticoid-free remission statistically significant, with 53% and 56% (weekly and every other week dosing, respectively) of tocilizumab patients having sustained remission at week 52, compared to 14% and 18% (26-week versus 52-week taper, respectively) of prednisone patients ($p < 0.001$).

III. In 2022 ACR/EULAR came out with updated classification criteria for giant cell arteritis. These criteria have demonstrated a sensitivity of 87% and a specificity of 94.8%. Current ACR guidelines are from 2021, therefore this new classification criteria are not included in the most current guidelines.

IV. The 1990 ACR criteria for giant cell arteritis have been demonstrated to have a sensitivity of 93.5% and a specificity of 91.2%. Newer criteria were proposed in 2012 by a collaborative effort of EULAR/ACR that aimed to reduce the need for arterial biopsy. The newer criteria thus have a lower sensitivity (68%) and specificity (78%) and have not been officially endorsed by the ACR.

V. While not entirely clear at this time what long-term effects tocilizumab use has on the underlying pathophysiology and outcomes in giant cell arteritis patients, treatment to maintain remission may prevent potential adverse effects associated with long-term glucocorticoid use.

Up to 50% of patients may experience return/relapse of giant cell arteritis after a successful taper of prednisone over one to two years, and in most cases, relapses do not lead to major adverse effects such as vision loss. Glucocorticoids are thus considered standard of care as first-line therapy and the primary treatment in patients presenting with giant cell arteritis. A guideline published by the British Society for Rheumatology (BSR)/British Health Professional in Rheumatology (BHPR) recommends that adjuvant therapy with methotrexate or other immunosuppressants be considered with recurrent relapses (started at the third relapse) or in patients who are unsuccessful with glucocorticoid taper.

VI. The 2021 American College of Rheumatology guidelines for GCA recommends starting high dose daily glucocorticoids, or tocilizumab with glucocorticoids or tocilizumab alone in newly diagnosed GCA. Patients with active extracranial large vessel involvement OR disease relapse with symptoms of cranial ischemia may start tocilizumab and glucocorticoids or start methotrexate with glucocorticoids if tocilizumab is not an option due to cost or tolerability. Guidelines have not been updated to include upadacitinib (Rinvoq).

VII. In a 2022 two-part study comparing new-onset compared to relapsing GCA treated with tocilizumab looking at 3-year timeline, 250 participants were randomized to receive tocilizumab weekly, tocilizumab every other week or placebo for 52 weeks (part 1), with a prednisone taper. In part two (open label), participants were treated at investigator discretion for 104 weeks. The primary endpoint in part 1 was the portion of patients achieving sustained glucocorticoid-free remission from week 12 to 52. In part two, the primary endpoint was maintenance of remission defined as absence of flare. A total of 250 participants completed part 1 and 215 participants transitioned to part 2. Of those, 184 patients (86%) were in clinical remission [TCZ QW, 81 (95%); TCW Q2W, 36 (90%); PBO, 67 (74%)] and stopped receiving blinded injections when they entered part 2. During part 2, 7 patients (3.3%) withdrew from the study for safety reasons, and 11 patients (5.1%) withdrew for non-safety reasons. Among the patients with new-onset disease, 49% in the TCZ QW group remained flare-free compared with 27% in the TCZ Q2W group and 28% in the PBO group. Participants with added tocilizumab experienced relapse after 575 (95% CI: 463) days. Whereas participants with glucocorticoids alone experienced relapse after 224 days (95% CI: 148, 322).

VIII. Tocilizumab can be used as initial treatment or as combination therapy with glucocorticoids in the first line setting. GCA is an emergent condition and patients diagnosed with GCA may be at great risk of sudden vision loss. Due to the urgency of the disease, patients are likely referred to seek urgent care and receive intravenous steroids to immediately reduce inflammation. Tocilizumab may be administered intravenously at point of care and patients may transition to subcutaneous injections thereafter.

IX. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

X. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease

control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XI. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References:

1. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med*. 2017;377(4):317-328.
2. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. *JAMA*. 2016;315(22):2442-2258.
3. Dasgupta B, Borg FA, Hassan N, et al. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology (Oxford).* 2010;49(8):1594-1597.
4. UpToDate, Inc. Treatment of giant cell arteritis. UpToDate [database online]. Waltham, MA. Last updated April 18, 2019. Available at: http://www.uptodate.com/home/index.html.
5. Nesher G, Breuer GS. Giant Cell Arteritis and Polymyalgia Rheumatica: 2016 Update. Rambam Maimonides Med J. 2016;7(4)
6. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8):1122-1128.
7. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
8. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
9. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
10. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Cryopyrin-Associated Periodic Syndromes (CAPS)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**

B. A diagnosis of a **cryopyrin-associated periodic syndrome (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID), familial cold autoinflammatory syndrome (FCAS) or Muckle-Wells syndrome (MWS); AND**
C. Member has documented laboratory evidence of a genetic mutation in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1), also known as NLRP

II. **Rilonacept (Arcalyst)** may be considered medically necessary when the following criteria below are met:
A. Member is being managed by or in consultation with a rheumatologist; **AND**
B. A diagnosis of **CAPS, including FCAS or MWS**; **AND**
C. Member has documented laboratory evidence of a genetic mutation in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1), also known as NLRP3

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 cryopyrin-associated periodic syndromes (CAPS) or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Anakinra (Kineret) is FDA approved for the treatment of CAPS, particularly neonatal-onset multisystem inflammatory disease (NOMID). Anakinra is also frequently employed in the other CAPS, including Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS), and can lead to rapid symptom improvement and a decrease in inflammatory markers. The pivotal trial in patients with NOMID was a single arm, prospective study that examined 43 patients treated with anakinra for up to 60 months. Outcomes included the use of a disease-specific symptom dairy as well as reduction in inflammatory markers, with improvement seen in both. Eleven patients also went through a withdrawal phase, in which symptoms/inflammatory markers worsened, followed by response again when anakinra was reinitiated. A retrospective review of 22 patients with CAPS (varied phenotypes), demonstrated efficacy of anakinra. All 15 patients treated with anakinra achieved serologic remission and resolution of symptoms (fever, rash, conjunctivitis, and rheumatic symptoms). Other small, observational studies have demonstrated similar improvements both serologically and symptomatically in patients with MWS and FCAS.
II. Rilonacept (Arcalyst) is FDA approved for treatment of CAPS, particularly in patients 12 years of age and older with familial cold autoinflammatory syndrome (FCAS) or Muckle-Wells syndrome (MWS). The relevant phase III trials included 47 patients who were randomized to either weekly rilonacept or placebo, with the first trial analyzing efficacy within a six-week follow-up, and the second looking at response after withdrawal of the agent in the same population. Disease activity via symptom score (0-10 scale) was significantly reduced within a few days of onset (84% rilonacept vs 13% placebo), with a decrease in inflammatory markers also observed. No data is

available for analysis in the NOMID population, and no head-to-head comparison with anakinra has been identified at this time.

References

1. Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2016.
2. Leslie KS, Lachmann HJ, Bruning E, et al. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. *Arch Dermatol.* 2006;142(12):1591-1597.
3. Hoffman HM, Throne ML, Amar NJ, et al. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum. 2008;58(8):2443-2452.
4. UpToDate, Inc. Cryopyrin-associated periodic syndromes and related disorders. UpToDate [database online]. Waltham, MA. Last updated May 17, 2019. Available at: http://www.uptodate.com/home/index.html.
5. Kuemmerle-deschner JB, Ozen S, Tyrrell PN, et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). *Ann Rheum Dis.* 2017;76(6):942-947.
6. Terreri MT, Bernardo WM, Len CA, et al. Guidelines for the management and treatment of periodic fever syndromes: Cryopyrin-associated periodic syndromes (cryopyrinopathies - CAPS). *Rev Bras Reumatol Engl Ed*. 2016;56(1):44-51.

Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist or immunologist; **AND**
   B. A diagnosis of Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS); **AND**
   C. Documentation of TNFRSF1A gene mutation; **AND**
      1. Member has chronic or recurrent fever flares, defined by three or more flares a year; **AND**
         i. Documentation of fever flares that last FIVE days or more; **AND**
         ii. Fever flares are accompanied by at least ONE of the following symptoms:
            a. Myalgia
            b. Rash
            c. Eye symptoms (e.g., conjunctivitis, periorbital edema)
            d. Limb pain
            e. Abdominal symptoms (e.g., pain, vomiting)
            f. Lymphadenopathy
            g. Chest pain; **AND**
   D. Provider attestation that other causes of recurrent fever have been ruled out (e.g., recurrent bacterial/viral infection, cyclic neutropenia, interferonopathies, etc.)

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 Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) (e.g., Ilaris, Arcalyst, etc) or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) is a rare genetic disorder that affects approximately one person per million. TRAPS diagnosis is confirmed by TNFRSF1A genetic mutation, in addition to prolonged fevers lasting 5 or more days and one additional clinical hallmark feature, such as myalgias, limb pain, abdominal symptoms (pain, vomiting), rash, headache, lymphadenopathy, chest pain, conjunctivitis, or periorbital edema. Underlying infections or neoplastic causes of fever must be ruled out prior to diagnosis. Given the rarity and complexity of diagnosis and management of TRAPS, the treatment of TRAPS must be initiated by, or in consultation with a rheumatologist.

II. Patients with three or more flares per year with inadequate response to oral glucocorticoids may be treated with prophylactic therapy with monoclonal antibodies that block IL-1 receptors. The 2021 European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR) Guidelines for Treatment of Interleukin-1 Mediated Autoinflammatory Diseases recognize both canakinumab (Ilaris) and anakinra (Kineret) as potential treatment options for prophylaxis of TRAPS over DMARDs.

III. Anakinra (Kineret) was the first IL-1 blocker successfully used in patients with TRAPS in small series and observational studies. One study was a small observational study with four children (mean age 9.1 years) and 1 adult (33 years) with TRAPS were treated with anakinra 1.5mg/kg/day. All patients had prompt responses with resolution of symptoms at 15 days. A systemic literature review identified 11 observational studies evaluating the use of anakinra (Kineret) in TRAPS. A total of 33% of patients achieved a complete response with anakinra at both short term and long-term follow-up. Other studies revealed patients with TRAPS that were successfully treated with anakinra had a complete clinical response and improvement in functional status. Studies evaluated anakinra (Kineret) at doses from 1-5mg/kg/day (max of 100mg daily) subcutaneously for pediatric patients 2 years and older with TRAPS.

IV. Given the rarity of the disease, the evidence to support efficacy and safety of anakinra (Kineret) in treatment of TRAPS is based on small series and observational studies. The guidelines do not make clear recommendations with anakinra (Kineret) as Canakinumab (Ilaris) is the only FDA-approved biologic for treatment of TRAPS but does recognize anakinra (Kineret) as a potential treatment option.

References

1. Kineret (anakinra) [prescribing information]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2020.
2. Gattorno M, Pelagatti MA, Meini A, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum. 2008;58(5):1516-1520.
3. ter Haar NM, Oswald M, Jeyaratnam J, et al. Recommendations for the management of autoinflammatory diseases. Ann Rheum Dis. 2015;74(9):1636-1644.
4. Romano M, Arici ZS, Piskin D, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. Ann Rheum Dis. 2022;81(7):907-921.
5. UpToDate, Inc. Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS). UpToDate [database online]. Waltham, MA. Last updated October 3, 2023.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

6. Kuemmerle-Deschner JB, Gautam R, George AT, Raza S, Lomax KG, Hur P. Systematic literature review of efficacy/effectiveness and safety of current therapies for the treatment of cryopyrin-associated periodic syndrome, hyperimmunoglobulin D syndrome and tumour necrosis factor receptor-associated periodic syndrome. RMD Open. 2020;6(2):e001227.

Familial Mediterranean Fever

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist, nephrologist, or gastroenterologist; **AND**
   B. A diagnosis of Familial Mediterranean Fever; **AND**
   C. Member has recurrent febrile episodes accompanied by at least ONE of the following:
      1. Peritonitis
      2. Synovitis or pleuritis
      3. Erysipelas-like erythema
      4. First degree relative with Familial Mediterranean Fever; **AND**
   D. Provider attestation that other causes of recurrent fever have been ruled out (e.g., recurrent bacterial/viral infection, cyclic neutropenia, interferonopathies, etc.); **AND**
   E. Treatment with colchicine 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. 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 Familial Mediterranean Fever (e.g., Ilaris, Arcalyst etc) or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent bouts of fever lasting a couple of days and serosal inflammation (e.g., peritonitis, pleuritis, pericarditis, synovitis) or erysipelas-like-erythema. Untreated FMF may lead to the development of secondary amyloidosis with eventual renal failure. Given the rarity and complexity of diagnosis and management of FMF, the treatment of FMF must be initiated by, or in consultation with a rheumatologist, nephrologist, or gastroenterologist.
II. The 2016 EULAR Recommendations for the Management of Familial Mediterranean Fever recommends colchicine as first line therapy and notes colchicine should be started as soon as a clinical diagnosis is made (grade A recommendation). The guidelines note that IL-1 blockers may be a treatment option based on case reports demonstrating successful use of anakinra (Kineret).
III. A systemic review and meta-analysis that evaluated 44 reports with 1399 FMF patients found that 60% (95% CI, 49-72%) of adults and 81% (95% CI, 72-89%) of pediatric patients achieved complete remission. At least one adverse event was observed in 25% (95% CI, 13-37%) of the

adult patients and 12% (95% CI, 3-21%) of the pediatric patients. Studies evaluated anakinra (Kineret) at doses of 1-5mg/kg/day (max of 100mg daily) subcutaneously for pediatric patients 2 years and older with FMF.

IV. Anakinra (Kineret) may be considered second line treatment after colchicine in treatment of FMF.

References

1. Kineret (anakinra) [prescribing information]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2020.
2. Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis. 2016;75(4):644-651.
3. Kilic B, Guler Y, Azman FN, Bostancı E, Ugurlu S. Efficacy and safety of anti-ınterleukin-1 treatment in familial Mediterranean fever patients: a systematic review and meta-analysis [published online ahead of print, 2023 Sep 28]. Rheumatology (Oxford). 2023;kead514.
4. UpToDate, Inc. Clinical manifestations and diagnosis of familial Mediterranean fever.a UpToDate [database online]. Waltham, MA. Last updated September 26, 2023.

Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD); **AND**
      1. Documentation of elevated immunoglobulin D (IgD) levels; **OR**
         i. Documentation of V3771 mutation in the mevalonate kinase gene; **AND**
   C. Documentation of fever flares that last four days or more; **AND**
   D. Fever flares are accompanied by at least ONE of the following symptoms:
      1. Chills
      2. Cervical lymphadenopathy
      3. Abdominal symptoms (e.g., pain, vomiting, diarrhea)
      4. Lymphadenopathy; **AND**
   E. Provider attestation that other causes of recurrent fever have been ruled out (e.g., recurrent bacterial/viral infection, cyclic neutropenia, interferonopathies, etc.)

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 Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) (e.g., Ilaris, Actemra, etc) or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Mevalonate Kinase Deficiency (MKD), formerly called Hyperimmunoglobulin D Syndrome (HIDS), is a rare, autosomal-recessive genetic disorder. Classic HIDS is due to compound heterozygous or homozygous V3771 mutation in the mevalonate kinase (MVK) gene. HIDS/MKD is characterized by recurrent febrile episodes lasting four or more days with chills and lymphadenopathy, abdominal pain, and elevated serum IgD levels above 14 mg/mL. Over 90% of patients have palpable lymphadenopathy during a febrile episode and 85% of patients present with abdominal pain (with or without vomiting and diarrhea). Elevated IgD levels are considered to be an epiphenomenon secondary to the inflammatory process and patients may not present with elevated IgD levels. When patients present with HIDS/MKD symptoms but do not have elevated IgD levels, genetic testing may be completed to confirm a diagnosis of HIDS/MKD but is not required if IgD levels are elevated. Underlying infections or neoplastic causes of fever must be ruled out prior to diagnosis. Given the rarity and complexity of diagnosis and management of HIDS/MKD, the treatment of HIDS/MKD must be initiated by, or in consultation with a rheumatologist.

II. Acute treatment for fever flares includes NSAIDs and corticosteroids. A 2015 retrospective study found that prophylactic use of anakinra (Kiineret) in HIDS/MKD resulted in 30% full response and 70% partial response in 10 patients. A systemic literature review identified 11 observational studies evaluating the use of anakinra (Kineret) in HIDS/MKD. A total of 11-30% of patients treated with anakinra achieved complete response at mid-term follow-up and 78% achieved partial response. Other observational studies revealed that anakinra decreased the AIDAI score and attained complete clinical response in 52% and functional status improvement in 81% of patients. Studies evaluated anakinra (Kineret) in pediatric patients 2 years and older with FMF.

III. The 2021 EULAR and ACR Guidelines for Treatment of Interleukin-1 Mediated Autoinflammatory Diseases recommend treatment with IL-1 antagonist as first line therapy for HIDS/MKD prophylaxis (grade C recommendation). Guidelines note that anakinra (Kineret) and canakinumab (Ilaris) have been used in children with HIDS/MKD with success, despite only canakinumab (Ilaris) having an FDA-approved indication in this space.

References

1. Kineret (anakinra) [prescribing information]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2020.
2. Favier LA, Schulert GS. Mevalonate kinase deficiency: current perspectives. Appl Clin Genet. 2016;9:101-110. Published 2016 Jul 20.
3. Rossi-Semerano L, Fautrel B, Wendling D, et al. Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. Orphanet J Rare Dis. 2015;10:19. Published 2015 Feb 15.
4. Kuemmerle-Deschner JB, Gautam R, George AT, Raza S, Lomax KG, Hur P. Systematic literature review of efficacy/effectiveness and safety of current therapies for the treatment of cryopyrin-associated periodic syndrome, hyperimmunoglobulin D syndrome and tumour necrosis factor receptor-associated periodic syndrome. RMD Open. 2020;6(2):e001227.

Recurrent Pericarditis

Initial Evaluation

I. **Rilonacept (Arcalyst)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   B. Member has a history of three or more episodes of pericarditis; **AND**
   C. Documentation that ALL of the following were ineffective, or all are contraindicated:

1. NSAID
2. colchicine
3. corticosteroids

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 another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Rilonacept (Arcalyst) is FDA approved for the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years of age and older.
II. According to the American College of Cardiology (ACC), pericarditis can be categorized as acute, incessant, recurrent, or chronic. An episode lasting ≥ 4-6 weeks without remission is defined to be incessant pericarditis, while pericarditis lasting > 3 months is defined to be chronic pericarditis. Key opinion leader input supports this classification and notes that for patients with an episode that appears to "recur" within 4 weeks is likely not a true recurrence but is still part of the initial episode or is incessant pericarditis.
III. The approval for this indication is based on findings from a phase III, multicenter, double-blind, event-driven, randomized-withdrawal design (RHAPSODY) trial (NCT03737110). Participants must have had at least one prior pericarditis episode meeting at least two of the following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation/PR-segment depression, or new/worsening pericardial effusion. During the 12-week run-in period, participants received rilonacept (Arcalyst). Participants were then randomized 1:1 to monotherapy rilonacept (Arcalyst) versus placebo during the double-blind withdrawal period. A total of 86 patients were enrolled in the trial who predominantly had idiopathic pericarditis (85%) and only 15% had post–cardiac-injury pericarditis. In order for the trial to have 90% power to evaluate the primary efficacy endpoint, 22 recurrence events would be needed to detect a statistical significance. A total of 25 primary efficacy end-point events had accrued when the randomized-withdrawal period closed. The primary efficacy endpoint of the study was time to pericarditis recurrence; however, during the withdrawal period, there were too few recurrent events noted in the rilonacept (Arcalyst) group to allow for median time calculation. The median time to the first adjudicated recurrence in the placebo group was 8.6 weeks (95% CI, 4.0 to 11.7). One notable secondary endpoint was the proportion of participants who maintained clinical response at 16 weeks with 81% of the rilonacept group (95% CI; 58-95) compared to 20% (95% CI; 6-44) in the placebo group.
IV. According to key opinion leader input and available information from Kiniksa, the place in therapy for rilonacept (Arcalyst) is in recurrent pericarditis only. According to a Journal of American College of Cardiology (JACC) review on the management of acute and recurrent pericarditis, in acute pericarditis, the injury to the pericardium leads to a cascade of inflammatory process where IL-1 receptor (IL-1R) occupies a central role. In this process, IL-1α

functions as an alarmin that is released during tissue injury and IL-1β gets released leading to amplification of the process. The rationale for the evaluation of rilonacept (Arcalyst) for recurrent pericarditis notes that this process is thought to stimulate the production of additional IL-1α and IL-1β which induces a self-perpetuating cycle of pericardial inflammation.

V. Both the 2015 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of pericardial diseases, and the 2020 American College of Cardiology review on the management of acute and recurrent pericarditis list treatment with NSAIDs/aspirin with colchicine for both acute pericarditis and recurrent pericarditis. According to ACC, anti-inflammatory therapy is the cornerstone of acute pericarditis. NSAIDs are recommended during an acute episode. Colchicine, which has a known anti-inflammatory effect, is recommended in patients with acute pericarditis in addition to aspirin or other NSAIDs. The benefit of colchicine is well established in both acute and recurrent pericarditis through various trials including, but not limited to, the CORE trial (2005), COPE trial (2005), and ICAP (2013). The ACC also notes that the efficacy of colchicine in recurrence has been shown in various studies. Key opinion leader input also supports the use of NSAIDs/aspirin and colchicine for both acute and recurrent pericarditis and that trial of these prior to rilonacept (Arcalyst) is clinically appropriate and aligns with evidence. Currently a 3-month course of colchicine is recommended for acute pericarditis; whereas, for recurrent pericarditis, a treatment course of at least 6 months is recommended.

VI. According to available information or guidelines for recurrent pericarditis, key opinion leader input and available data for the use of rilonacept (Arcalyst) in recurrent pericarditis, NSAIDs and colchicine (≥ 6 months) remain the standard of care for the treatment for initial recurrence of pericarditis. Low-dose corticosteroids are also often used in the treatment of recurrent pericarditis and are associated with a high treatment success rate per ACC. Currently, the place in therapy for rilonacept (Arcalyst) can be considered for patients with multiple recurrence of pericarditis, and/or for patients where further use of NSAIDs, colchicine, and a low-dose corticosteroid are not clinically appropriate.

References

1. Arcalyst [package insert]. London, UK: Kiniksa Pharmaceuticals (UK), Ltd.; 2021.
2. Klein AL, Imazio M, Crèmer P, et al. Phase 3 Trial of Interleukin-1 Trap Rilonacept in Recurrent Pericarditis. N Engl J Med 2021;384:31-41. DOI: 10.1056/NEJMoa2027892
3. Chiabrando JG, Bonaventura A, Vecchie A. Management of Acute and Recurrent Pericarditis: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75(1):76–92.
4. Adler Y, Charron P, Imazio M, et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC). European Heart Journal.2015;36:2921–2964.
5. Chiabrando JG, Bonaventura A, Vecchié A, et al. Management of Acute and Recurrent Pericarditis: JACC State-of-the-Art Review. 2020; 75(1):76-92. doi.org/10.1016/j.jacc.2019.11.021.
6. Klein AL, Imazio M, Brucato A, et al. RHAPSODY: Rationale for and design of a pivotal Phase 3 trial to assess efficacy and safety of rilonacept, an interleukin-1α and interleukin-1β trap, in patients with recurrent pericarditis. J. Am. Heart Assoc. 2020: 228: 81-90. doi.org/10.1016/j.ahj.2020.07.004.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

Initial Evaluation

I. **Tocilizumab-aazg (Tyenne)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a pulmonologist or rheumatologist; **AND**

B. Tocilizumab (Actemra, Tyenne) will not be used in combination with nintedanib (Ofev) or pirfenidone (Esbriet); **AND**
C. A diagnosis of **Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)** when all of the following are met:
    1. The diagnosis is confirmed by a high resolution computed tomographic (HRCT) scan; **AND**
    2. Treatment with immunomodulators (e.g., mycophenolate mofetil or cyclophosphamide) has been ineffective, contraindicated, or not tolerated.

II. **Brand Actemra** 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 a biosimilar product; **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**
        i. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
            1. tocilizumab-aazg (Tyenne) has been tried; **OR**
        ii. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
        iii. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
            1. Was life-threatening; **OR**
            2. Required hospitalization; **OR**
            3. Required intervention to prevent impairment or damage

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 member has exhibited improvement or stability of disease symptoms (e.g., sustained forced vital capacity (%FVC) decline or minimal decline in diffusing capacity of the lung for carbon monoxide (DLCO)); AND
    A. If the request is for **Brand Actemra**: 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 biosimilar; **AND**

B. 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**
    1. The member experienced a documented severe intolerance to an adequate trial of the biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
        i. tocilizumab-aazg (Tyenne) has been tried; **OR**
    2. The member started therapy with the reference drug and has chart note documentation of an allergic reaction to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage (*as confirmed by a health plan pharmacist*); **OR**
    3. The member started therapy with the reference drug and has chart note documentation of a serious adverse reaction to a biosimilar that caused one or more of the following (*as confirmed by a health plan pharmacist*), indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage

Supporting Evidence

I. Scleroderma-associated interstitial lung disease (SSc-ILD) is a chronic lung disease in which fibrosis builds up in the lungs in a person diagnosed with systemic sclerosis (SSc). Direct pulmonary involvement in SSc is the main cause of death in patients with SSc. Early diagnosis, severity assessment, prediction of progression, and appropriate treatment of SSc- ILD is necessary to achieve the best possible patient outcomes. Goals of treatments include optimizing therapy, slowing disease progression, and prolonging time to progression and survival.

II. The presence of SSc-ILD is defined by the identification of fibrotic features on high- resolution CT (HRCT) scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.

III. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).

IV. Decisions to initiate or advance treatment often take into consideration the likelihood of progression, patient comorbidities, risk of toxicities, and current data on efficacy. Patients are treated based on expert-derived recommendations for the management of organ-specific manifestations. The European expert consensus published in 2020 recommends immunosuppressive therapies in severe or progressive ILD, including mycophenolate mofetil, cyclophosphamide, or nintedanib (Ofev) in patients requiring pharmacotherapy.

V. Nintedanib (Ofev) is approved to slow the rate of decline in pulmonary function in patients with SSc-ILD. Given its recent approval in 2019, its role in clinical practice (e.g., timing of initiation, use as add-on or monotherapy) for patients with SSc-ILD has not been well-defined.

VI. There is no evidence to suggest that combination therapy of tocilizumab (Actemra) and nintedanib (Ofev) or pirfenidone (Esbriet) will be safe or effective when used to treat Scc-ILD.

VII. The FDA has approved tocilizumab (Actemra) for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD. The decision was based on the two clinical trials: the focuSSced Phase 3 trial and the Phase 2/3 faSScinate trial.

A. The focuSSed trial: A randomized, double-blind, placebo-controlled trial enrolled 212 participants >18 years of age to receive tocilizumab (Actemra) 145 mg subcutaneously once weekly (N=104) or placebo (N=106) for at least 48 weeks. Participants were excluded if they had severe restricted airway disease, including a percentage of predicted forced vital capacity (FVC% predicted) ≤ 55%, DLCO ≤45, or PAH WHO class 2 or higher. Patients were not on immunomodulating therapy (mycophenolate, cyclophosphamide) during enrollment.

a. The primary endpoint, the difference in change from baseline in modified Rodnan skin score (mRSS), was not met. Post-hoc analyses were performed to evaluate results within the subgroups of participants with and without SSc-ILD. Results of the FVC secondary endpoints support the effectiveness of tocilizumab (Actemra) in reducing the rate of progressive loss of lung function in SSc-ILD.

	Overall population		Subgroup without SSc-ILD*		SSc-ILD subgroup*	
	Placebo	Tocilizumab	Placebo	Tocilizumab	Placebo	Tocilizumab
Number of patients	106	104	36	34	68	68
Change from baseline in mRSS score						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
Difference in LSM (95% CI)†	-1.73 (-3.78, 0.32); p = 0.10		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	
Change from baseline in ppFVC (%)						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
Difference in LSM (95% CI)†	4.20 (2.00, 6.40); p=0.0002		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
Change from baseline in observed FVC (mL)						
LSM	-190	-24	-53	-11	-255	-14
Difference in LSM (95% CI)†	167 (83, 250); p = 0.0001		43 (-60, 145)		241 (124, 358)	

*Post-hoc results are shown for this subgroup. Four patients had ILD status missing at baseline.
†Difference in LSM (least means squared) between tocilizumab and placebo populations at week 48

b. Subjects with SSc-ILD treated with tocilizumab (Actemra) had a smaller decline in mean ppFVC than placebo (0.07% vs. -6.4%, mean difference 6.47%), and a smaller decline in FVC compared to placebo (mean change -14mL vs. -255mL, mean difference 241mL).

B. The faSSinate trial was a randomized, double-blind, placebo-controlled trial which enrolled 87 participants > 18 years of age with SSc to receive tocilizumab (Actemra) 145 mg subcutaneously once weekly (N=44) or placebo (N=43). Participants were excluded if they had severe restricted airway disease, including a percentage of predicted forced vital capacity (FVC% predicted) ≤ 50%, DLCO ≤40, or PAH WHO class 2 or higher. Patients were not on immunomodulating therapy (mycophenolate, cyclophosphamide) during enrollment. The primary endpoint, the difference in change from baseline in modified Rodnan skin score (mRSS) at week 24, was not met. Results of the ad-hoc FVC secondary endpoints support the effectiveness of tocilizumab (Actemra) in reducing the rate of progressive loss of lung function in SSc at week 48.

	ITT population	
	Placebo	Tocilizumab
mRSS change from baseline at week 48		
Number of patients	44	43
LSM	-2.10	-5.46
Difference in LSM (95% CI)	-3.36 (-7.3,0.32); p=0.0726	
Change from baseline in ppFVC (%) at week 48		
Number of patients	26	28
LSM	-6.31	-2.04
Difference in LSM (95% CI)	4.27 (0.68,7.78); p = 0.02	
Change from baseline in observed FVC (mL) at week 48		
Number of patients	27	28
LSM	-230	-91
Difference in LSM (95% CI)	138 (-2,279); p =0.05	

VIII. No new or unexpected safety findings were observed in both studies. Adverse events observed in subjects receiving tocilizumab (Actemra) were consistent with the known safety profile in other indications.

IX. The impact of tocilizumab (Actemra) on disease involvement in lung tissue as examined by CT scans has not been evaluated.

X. Safety and efficacy of tocilizumab (Actemra) in the setting of SSc-ILD has not been established in patients <18 years of age.

XI. Safety and efficacy of tocilizumab (Actemra) has not been established in other etiologies of ILD (e.g., idiopathic pulmonary fibrosis, non-specific interstitial pneumonia) and would remain experimental or investigational in non-SSc ILD.

XII. Biologic products are large, complex molecules that are made from living sources, such as bacteria, yeast, and animal cells. Because these products come from living organisms, biologics inherently contain slight variations from batch to batch. Although there is variability within the product, whether a reference drug or biosimilar, this is not anticipated to produce a difference in product effectiveness overall based on the high testing standards set by the FDA.

XIII. Biosimilars are biologic medications that are highly similar to and have no clinically meaningful differences from an existing FDA-approved biologic, known as a reference drug. Biosimilars are made of the same type of living sources, are administered in the same way and have the same strength, dosage, potential treatment benefits, and potential side effects as the reference drug. Due to the complex nature and living nature of biologic products, biosimilars cannot be copied exactly from the reference drug and may contain a mix of many slight variations of a protein. However, this variability is not anticipated to result in a difference in effectiveness or disease control in patients that are switching from the reference drug to the biosimilar based on a rigorous evaluation that biosimilar products go through to ensure their safety, effectiveness and quality.

XIV. Data from four robust meta-analyses evaluating the impact of switching from a reference drug to a biosimilar, between biosimilars, or from a biosimilar to reference drug demonstrated that there is no significant difference in clinical, safety, or immunogenicity responses between those that switch products and those that are maintained on the reference drug or single biosimilar product. One analysis that evaluated the effect of successive switches of biosimilar products (the second switch occurring 24 months after switch to first biosimilar) did not increase the risk of immunogenicity compared to previous studies that evaluated the use of one biosimilar. Another analysis that focused heavily on safety outcomes found that the unadjusted overall risk (OR) for

the switching group compared to non-switching group for all three safety events of death, serious adverse event (SAE), and discontinuation was 1.003, 1.102, and 0.974, respectively; p-value >0.05 was reported for each safety outcome, indicating no significant difference between groups. Although another analysis concluded that switching from a reference drug to biosimilar for non-medical reasons (i.e., insurance formulary status change) was associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events (AEs), this rate was comparable to yearly discontinue rates of the original TNF-inhibitor. These results confirm that switching from a reference drug to a biosimilar product pose no additional risks for safety, efficacy, or immunogenicity for patients, and it is not expected that such a change puts the patient at undue risk for inadequate disease management.

References

1. Actemra® [prescribing information]. South San Francisco, CA: Genentech; March 2021
2. Khanna D, Lin CJF, Furst DE, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med.* 2020 Oct;8(10):963-974. doi: 10.1016/S2213-2600(20)30318-0. Epub 2020 Aug 28. Erratum in: *Lancet Respir Med.* 2020 Oct;8(10):e75. Erratum in: *Lancet Respir Med.* 2021 Mar;9(3):e29. PMID: 32866440.
3. Khanna D, Denton CP, Jahreis A, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial [published correction appears in *Lancet*. 2018 Apr 7;391(10128):1356]. Lancet. 2016;387(10038):2630-2640. doi:10.1016/S0140-6736(16)00232-4
4. NIH National Center for Advancing Translational Sciences. Systemic Scleroderma. Accessed June 7, 2021. https://rarediseases.info.nih.gov/diseases/9748/systemic-scleroderma
5. Khanna D, Tashkin DP, Denton CP, Renzoni EA, Desai SR, Varga J. Etiology, Risk Factors, and Biomarkers in Systemic Sclerosis with Interstitial Lung Disease. *Am J Respir Crit Care Med*. 2020 Mar 15;201(6):650-660. doi: 10.1164/rccm.201903-0563CI. PMID: 31841044; PMCID: PMC7068837.
6. Bernstein EJ, Huggins JT, Hummers LK, Owens GM. Systemic sclerosis with associated interstitial lung disease: management considerations and future directions. *Am J Manag Care.* 2021;27(7 Suppl):S138-S146. doi:10.37765/ajmc.2021.88656

Polymyalgia Rheumatica (PMR)

Initial Evaluation

I. **Sarilumab (Kevzara)** may be considered medically necessary when the following criteria are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **polymyalgia rheumatica** when the following are met:
      1. Presence of the following:
         I. Age at disease onset of at least 50 years; **AND**
         II. Presence of bilateral shoulder and/or pelvic girdle pain lasting at least 2 weeks; **AND**
         III. Presence of morning stiffness > 45 minutes; **AND**
         IV. Elevated CRP or ESR; **AND**
         V. Previous treatment with at least one glucocorticoid (i.e., prednisone, hydrocortisone, methylprednisolone, etc.) and attempted dose reduction/taper 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. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of elevated inflammatory markers the CRP and ESR, improvement of bilateral shoulder and/or pelvic girdle pain, reduction of duration of daily morning stiffness)

Supporting Evidence

I. Sarilumab (Kevzara) is FDA-approved for adult patients with Polymyalgia rheumatica based off results of the SAPHYR study (n=118), a phase 3, randomized, double-blind placebo-controlled trial evaluating the efficacy of sarilumab in patients with PMR as assessed by the proportion of subjects with sustained remission for sarilumab with a shorter corticosteroid (CS) tapering regimen as compared to placebo with a longer CS tapering regimen. The duration was approximately 62 weeks which included a 4-week screening period, 52-week treatment period and 4-week follow-up period. Sustained remission rate was significantly higher in the sarilumab arm vs the placebo arm (28.3% vs 10.3%; P=0.0193). With regards to safety of sarilumab compared to placebo in the SAPHYR trial, more patients had adverse events in the sarilumab arm (94.9% vs 84.5% for sarilumab vs placebo), however, less patients experienced serious adverse events in the sarilumab arm when compared to placebo (20.7% vs 13.6%). The common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia (15.3%), leukopenia (6.8%), constipation (6.8%), rash pruritus (5.1%), myalgia (6.8%), fatigue (5.1%), and injection site pruritus (5.1%).

II. The diagnosis and management of PMR requires detailed clinical examination. Given the complexities of diagnosis and treatment of this condition, supervision of treatment by a rheumatologist is required.

III. According to the European League Against Rheumatism/American College of Rheumatology Collaborative Initiative (EULAR/ACR) classification criteria for PMR, patients are required to be age 50 years and older to be considered for a diagnosis of PMR. The typical age of onset of the disease is 60-70 years old, and it is unlikely that a patient be diagnosed with PMR under the age of 50 years old. Other diagnoses should be considered and ruled out if a patient presents with symptoms under the age of 50. Additionally, the safety and efficacy of Kevzara in patients less than 50 years old have not been established in patients with PMR

IV. The presence of bilateral shoulder and/or hip pain are hallmark presenting symptoms for PMR. Within EULAR/ACR classification criteria for PMR and in the SAPHYR trial, bilateral shoulder and/or hip pain is required for diagnosis. Although morning stiffness is not mutually exclusive to PMR, the presence of morning stiffness for greater than > 45 minutes is very strong predictor of a PMR diagnosis and is commonly utilized in clinical practice.

V. Elevation of acute phase reactants such as CRP and/or ESR are strong predictors of diagnosis of PMR and are requirements for diagnosis within the EULAR/ACR classification criteria. All patients included in the SAPHYR trial must have had elevation in either CRP or ESR, defined as CRP> 10mg/L and/or ESR> 30mm/hour.

VI. Trial of a corticosteroid (e.g., prednisone) is considered first-line therapy and the standard of care for patients diagnosed with PMR. If patients exhibit a response/sustained remission with corticosteroids, a dose reduction or taper may be implemented to reduce long term exposure steroids. Sarilumab (Kevzara) is only indicated for patients who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper. Every patient within the SAPHYR trial were required to start prednisone and undergo a taper before starting sarilumab or placebo. The efficacy and safety of sarilumab in the first-line setting prior to corticosteroid use have not been established at this time.

References

1. Sarilumab (Kevzara) [Prescribing Information]. Bridgewater, NJ; Sanofi-Aventis. May 2017.
2. Dasgupta B, Unizony S, Warrington KJ*, et al* LB0006 Sarilumab in patients with relapsing polymyalgia rheumatica. A phase 3, multicenter, randomized, double blind, placebo controlled trial (SAPHYR) *Annals of the Rheumatic Diseases* 2022;81:210-211.
3. Evaluation of the Efficacy and Safety of Sarilumab in Patients With Polymyalgia Rheumatica. Results posted. Available at: https://clinicaltrials.gov/ct2/show/NCT03600818
4. Dejaco C, Singh YP, Perel P*, et al* 2015 Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative *Annals of the Rheumatic Diseases* 2015;74:1799-1807.
5. Manzo C. Messages from the history of polymyalgia rheumatica. *Reumatologia*. 2021;59(6):425-426. doi:10.5114/reum.2021.110221Lee JH, Choi ST, Kim JS, et al. Clinical characteristics and prognostic factors for relapse in patients with polymyalgia rheumatica (PMR). *Rheumatol Int*. 2013;33(6):1475-1480. doi:10.1007/s00296-012-2580-4
6. Hernández-Rodríguez J, Cid MC, López-Soto A, Espigol-Frigolé G, Bosch X. Treatment of polymyalgia rheumatica: a systematic review. *Arch Intern Med*. 2009;169(20):1839-1850. doi:10.1001/archinternmed.2009.352
7. Floris, A., Piga, M., Chessa, E., Congia, M., Erre, G. L., Angioni, M. M., Mathieu, A., & Cauli, A. (2022). Long-term glucocorticoid treatment and high relapse rate remain unresolved issues in the real-life management of polymyalgia rheumatica: a systematic literature review and meta-analysis. Clinical rheumatology, 41(1), 19–31. https://doi.org/10.1007/s10067-021-05819-z
8. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, Matteson EL, Dasgupta B. Current evidence for therapeutic interventions and prognostic factors in polymyalgia rheumatica: a systematic literature review informing the 2015 European League Against Rheumatism/American College of Rheumatology recommendations for the management of polymyalgia rheumatica. Ann Rheum Dis. 2015 Oct;74(10):1808-17. doi:10.1136/annrheumdis-2015-207578. PMID: 26359489
9. Dasgupta B, Cimmino MA, Maradit-Kremers H, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis*. 2012;71(4):484-492. doi:10.1136/annrheumdis-2011-200329
10. Herndon TM, Ausin C, Brahme NN, et al. Safety outcomes when switching between biosimilars and reference biologics: A systematic review and meta-analysis. PLOS ONE. 2023; 18 (10): 1-15.
11. Liu Y, Skup M, Yang M, et al. Discontinuatino and switchback after non-medical switching from originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimiars: A meta-analysis of real-world studies from 2012 to 2018. Adv Ther. 2022; 39: 3711 – 3734.
12. Lauret A, Molto A, Abitbol V, et al. Effects of successive switches to different biosimilars infliximab on immunogenicity in chronic inflammatory diseases in daily clinical practice. Seminars in Arthritis and Rheumatism. 2020; 50: 1449-1456.
13. Ascef BO, Almeida MO, Medeiros-Riberio AC, et al. Impact of switching between reference biologics and biosimilars of tumor necrosis factor inhibitors for rheumatoid arthritis: a systematic review and network meta-analysis. Scientific Reports. 2023; 13: 13699.

Investigational or Not Medically Necessary Uses

I. Cutaneous Sarcoidosis
   A. Apremilast and adalimumab have both been analyzed in this disease state. Efficacy data is limited to case reports and small studies at this time. One small RCT of adalimumab (n = 16) demonstrated a decrease in target lesion area compared to placebo. Similarly, a small observational study in 15 patients receiving apremilast demonstrated a reduction in induration at week 12 compared to baseline. Only one investigator performed the lesion assessment in this study, and similar to adalimumab, further larger scale, randomized studies are needed to fully establish efficacy of these agents.

II. Deficiency of IL-1 Receptor Antagonist (DIRA)
   A. Although anakinra (Kineret) is FDA approved for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA), the safety and efficacy data that led to FDA approval is considered to be of low quality. This approval is based on safety data from a National Institute of Allergy and Infectious Diseases (NIAID) study of nine patients with IL1RN mutations (17-I-0016). This study was neither designed nor powered to evaluate the

efficacy of anakinra (Kineret) for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA). This study was part of a larger ongoing NIAID sponsored study on patients NOMID/CAPS, DIRA, CANDLE, SAVI, NLRC4-MAS, Still's Disease, and with other yet undifferentiated autoinflammatory diseases. This study is designed to identify the disease pathogenesis, including clinical, immunological, genetic and endocrinological characteristics of the disease. Currently, this indication is considered experimental and investigational due to the ongoing study and limited efficacy data for this indication.

B. DIRA is a recently described recessively inherited autoinflammatory disease linked to activation of the IL-1 pathway. DIRA is to not be confused with DITRA (deficiency of interleukin-36 receptor antagonist) which usually results to generalized pustular psoriasis. Children with DIRA usually present with the following within the first weeks of life: symptoms of systemic inflammation (such as elevation of acute phase reactants and low-grade fever), pustular rashes, joint swelling, oral mucosal lesions and severe bone pain when being picked up. Currently, there are no other FDA approved agents approved for the treatment of DIRA. Patients who were evaluated in the NIAID sponsored study were previously treated with antibiotics, NSAIDs, corticosteroids, IVIG, and DMARDs (e.g. methotrexate, azathioprine, etc).

III. Graft Versus Host Disease (GVHD)

A. A number of observational trials have examined etanercept in acute GVHD. Treatment regimens vary significantly between these observational studies. Data from a pilot and phase II trial pooled against observational data of standard of care patients receiving standard of care with steroids observed a higher complete response rate in those treated with etanercept. The results are significantly limited, however, by the observational, nonrandomized nature and thus prospective, randomized trials are needed to fully establish possible benefit in GVHD. The use of tocilizumab has also been studied in a small population (n = 8) with refractory GVHD. While response was observed in four of the six tocilizumab treated patients, the limited sample size is insufficient to confirm efficacy at this time.

B. The safety and efficacy of the self-administered formulation of abatacept (Orencia) has not been evaluated. The intravenous form of abatacept (Orencia) is FDA-approved for the prevention or prophylaxis of acute graft vs. host disease (aGVHD). The FDA-approval of intravenous abatacept (Orencia) in aGVHD was based on two studies; a double-blind, placebo-controlled trial that showed survival benefit over placebo when used in combination with other immunosuppressive drugs; and a registry-based evaluation that compared patients that received abatacept (Orencia) in addition to conventional immunosuppressant therapy vs. conventional immunosuppressive therapy alone. The study observed to abatacept (Orencia) to have a survival benefit when used with conventional immunosuppressive treatments. The FDA-approved dose is 10 mg/kg IV over 60 minutes the day prior to stem cell transplantation, as well as days 5, 14, 28 days after transplantation, which conveniently overlaps with the expected inpatient stay following stem cell transplantation. Accurate dosing may only be achieved with the intravenous formulation. In addition to having unknown safety and efficacy, the self-administered formulation would have a greater injection burden, greater medication waste, and greater cost compared to the intravenous formulation. No other biologic therapies have been evaluated for this condition.

IV. Grave's Ophthalmopathy

A. A small, phase III RCT (n = 32) analyzed tocilizumab use compared to placebo in this disease state. A statistically significant reduction was observed in the clinical activity score

from baseline by week 16, but given the small sample size, the American Academy of Ophthalmology has recommended that larger studies be completed to fully establish safety and efficacy for this indication.

V. Guttate Psoriasis
    A. In this form of psoriasis, case reports suggest that the use of TNF inhibitors may induce flares when used. 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 or targeted DMARDs in this setting at this time.

VI. Interstitial Cystitis
    A. TNF inhibitors such as adalimumab and certolizumab pegol have been studied in small, phase III RCTs. In the study of certolizumab pegol, no difference was observed in interstitial cystitis compared to placebo at week 2. Secondary outcomes indicate benefit may occur in this population by week 10-18 of therapy. A similar study was completed with adalimumab, with no statistical difference observed in the primary outcome at week 12 compared to placebo. Further studies are needed to analyze efficacy in this population.

VII. Lupus Nephritis and Systemic Lupus Erythematosus (SLE)
    A. Abatacept was analyzed in a large phase III RCT (n =695) in patients with lupus nephritis and in combination with mycophenolate and steroids. No difference was observed in the primary outcome of complete renal response at one year compared to placebo. Studies utilizing ustekinumab are currently recruiting in patients with SLE.

VIII. Osteoarthritis
    A. Infliximab and adalimumab have been examined for use in patients with erosive, hand osteoarthritis. Mixed results have been seen so far. Open-label, observational studies of infliximab have shown potential benefit, while studies with adalimumab have been inconclusive. For instance, in a RCT of 60 patients, the difference in proportion of active disease in the adalimumab versus placebo group was not statistically significant. Further studies are needed to establish safety and efficacy.

IX. Palmoplantaris **Pustulosis**/Pustulosis palmaris et plantaris
    A. It is not uncommon for forms of pustulosis to coexist with plaque psoriasis/psoriasis vulgaris; however, in absence of a covered indication and when associated criteria are met, use of non-biologic and biologic therapies in the setting of pustulosis is considered experimental and investigational.
    B. A small placebo-controlled (n =15) of etanercept in palmoplantaris pustolosis supported potential efficacy of TNF inhibitors. Observations have also occurred demonstrating worsening of this disease with use of TNF inhibitors. Other biologics, such as the use of IL-12/IL-23 inhibitor ustekinumab, did not demonstrate benefit in palmoplantaris pustolosis. A phase II study has analyzed guselkumab, and case reports of IL-1 inhibitors such as anakinra have been reported, though further study is needed to confirm the use of biologics in this population.

X. Polymyositis and Dermatomyositis
    A. One phase III trial is currently recruiting to analyze abatacept in patients with polymyositis and dermatomyositis. Anakinra has also been examined in a single group study (n = 15). Decrease in certain inflammatory markers was observed, however, the clinical and patient-centered outcomes of anakinra use in this population requires further analysis. Another single-group, non-randomized trial (n = 13) looked at infliximab use in this

population. None of the included patients had improvement in muscle strength by manual, and only two patients saw any improvement in disease activity scores.

XI. Pulmonary Sarcoidosis
    A. The TNF inhibitors infliximab, adalimumab, and etanercept have been studied to some extent in pulmonary sarcoidosis. A phase II study (n = 138) saw a statistically significant increase in functional vital capacity at week 24 compared to placebo, however, the effect size was small with a mean increase of just 2.5% from baseline. A small, open-label phase II study with etanercept was terminated early due to an excessive number of treatment failures. Case reports of adalimumab exist, and one study which examined 18 patients who switched after infliximab use saw improvement in just over one-third of patients, however, further prospective, randomized trials would be needed to fully establish safety and efficacy.
XII. Pyoderma gangrenosum
    A. Case reports of the use of TNF inhibitors are available in this patient population. Most reports have involved patients with another indication for a TNF inhibitor, such as IBD or RA. A Phase III trial for this disease state is currently recruiting in Japan.
XIII. Sciatica
    A. One small RCT has examined adalimumab in patients with acute/severe radicular leg pain and imagine-confirmed lumber disc herniation. Of the 61 patients, a statistically significant, though small effect, was seen at week 6 compared to placebo. At the 6 month follow up, the statistically significant difference was lost. While a difference in surgical discectomies was also seen,
XIV. Systemic sclerosis (scleroderma)
    A. A phase III RCT (n =212) comparing tocilizumab to placebo in patients with systemic sclerosis did not observe a statistically significant difference in change from baseline to week 48 in the primary outcome in the Modified Rodnan Skin Score (mRSS).
XV. Sjogren's Syndrome
    A. Studies with TNF inhibitors etanercept and infliximab have not demonstrated benefit in Sjogren's syndrome. A RCT (n = 103) found no difference in disease activity between infliximab and placebo by week 22. Likewise, a smaller RCT (n = 28) found no statistical difference with etanercept versus placebo at 12 weeks after treatment initiation. Small, open-label studies have also been done with abatacept, though sample size has been small, and data has been mixed, with one trial demonstrating improvement in salivary gland biopsy and extraglandular manifestations, and one showing no change in tear flow or improvement in other symptoms.
XVI. Wegener's Granulomatosis
    A. One phase III RCT (n = 181) exists for the use of etanercept in patients with Wegener's Granulomatosis. Compared to standard of care (steroids plus cyclophosphamide or methotrexate), patient on etanercept demonstrated an initial sustained remission for at least six months that was not statistically different from standard of care. Likewise, a large proportion of patients lost response over the 27 months mean follow up period. An open-label study with infliximab (n = 16) has also been completed, with similar response rates to that described above in the etanercept study.
XVII. Secukinumab in Rheumatoid Arthritis
    A. Three phase III studies (NURTURE-1, REASSURE, REASSURE-2) evaluated the use of secukinumab in patients with rheumatoid arthritis. Novartis is not planning to pursue approval for secukinumab as the trials were terminated due to lack of comparative efficacy. Given the availability of other FDA approved options in this setting with

established safety profiles and signals of efficacy, there is insufficient data to allow a standard path to coverage for Cosentyx in rheumatoid arthritis.

XVIII. Infliximab-dyyb (Infliximab)

A. Infliximab-dyyb (Zymfentra) is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis and Crohn's disease. Intravenous (IV) infliximab formulation is clinically comparable in efficacy and safety to the SC formulation and is the preferred product which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

References

1. Melikoglu M, Fresko I, Mat C, et al. Short-term trial of etanercept in Behçet's disease: a double blind, placebo controlled study. *J Rheumatol.* 2005;32(1):98-105.
2. Vallet H, Riviere S, Sanna A, et al. Efficacy of anti-TNF alpha in severe and/or refractory Behçet's disease: Multicenter study of 124 patients. *J Autoimmun*. 2015;62:67-74.
3. Pariser RJ, Paul J, Hirano S, Torosky C, Smith M. A double-blind, randomized, placebo-controlled trial of adalimumab in the treatment of cutaneous sarcoidosis. *J Am Acad Dermatol.* 2013;68(5):765-773.
4. Baughman RP, Judson MA, Ingledue R, Craft NL, Lower EE. Efficacy and safety of apremilast in chronic cutaneous sarcoidosis. *Arch Dermatol.* 2012;148(2):262-264.
5. Levine JE, Paczesny S, Mineishi S, et al. Etanercept plus methylprednisolone as initial therapy for acute graft-versus-host disease. *Blood.* 2008;111(4):2470-2475.
6. Drobyski WR, Pasquini M, Kovatovic K, et al. Tocilizumab for the treatment of steroid refractory graft-versus-host disease. *Biol Blood Marrow Transplant.* 2011;17(12):1862-1868.
7. Allen RC. Tocilizumab shows promise in refractory Graves orbitopathy. American Academy of Ophthalmology website. https://www.aao.org/editors-choice/tocilizumab-shows-promise-in-refractory-graves-orb. Published December 4, 2018. Accessed June 21, 2019.
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. Bosch PC. A Randomized, Double-blind, Placebo-controlled Trial of Certolizumab Pegol in Women with Refractory Interstitial Cystitis/Bladder Pain Syndrome. *Eur Urol*. 2018;74(5):623-630.
10. Bosch PC. A randomized, double-blind, placebo controlled trial of adalimumab for interstitial cystitis/bladder pain syndrome. *J Urol*. 2014;191(1):77-82
11. 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.
12. Güler-yüksel M, Allaart CF, Watt I, et al. Treatment with TNF-α inhibitor infliximab might reduce hand osteoarthritis in patients with rheumatoid arthritis. *Osteoarthr Cartil*. 2010;18(10):1256-1262.
13. Verbruggen G, Wittoek R, Vander cruyssen B, Elewaut D. Tumour necrosis factor blockade for the treatment of erosive osteoarthritis of the interphalangeal finger joints: a double blind, randomised trial on structure modification. *Ann Rheum Dis*. 2012;71(6):891-898.
14. Bissonnette R, Poulin Y, Bolduc C, et al. Etanercept in the treatment of palmoplantar pustulosis. *J Drugs Dermatol.* 2008;7(10):940-946.
15. Bissonnette R, Nigen S, Langley RG, et al. Increased expression of IL-17A and limited involvement of IL-23 in patients with palmo-plantar (PP) pustular psoriasis or PP pustulosis; results from a randomised controlled trial. *J Eur Acad Dermatol Venereol.* 2014;28(10):1298-1305.
16. Kreiner F, Galbo H. Effect of etanercept in polymyalgia rheumatica: a randomized controlled trial. *Arthritis Res Ther.* 2010;12(5):R176.
17. Salvarani C, Macchioni P, Manzini C, et al. Infliximab plus prednisone or placebo plus prednisone for the initial treatment of polymyalgia rheumatica: a randomized trial. *Ann Intern Med.* 2007;146(9):631-639.
18. Zong M, Dorph C, Dastmalchi M, et al. Anakinra treatment in patients with refractory inflammatory myopathies and possible predictive response biomarkers: a mechanistic study with 12 months follow-up. *Ann Rheum Dis.* 2014;73(5):913-920.
19. Dastmalchi M, Grundtman C, Alexanderson H, et al. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. *Ann Rheum Dis.* 2008;67(12):1670-1677.

20. Baughman RP, Drent M, Kavuru M, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med.* 2006;174(7):795-802.
21. Crommelin HA, Van der burg LM, Vorselaars AD, et al. Efficacy of adalimumab in sarcoidosis patients who developed intolerance to infliximab. *Respir Med.* 2016;115:72-77.
22. Reddick CL, Singh MN, Chalmers RJ. Successful treatment of superficial pyoderma gangrenosum associated with hidradenitis suppurativa with adalimumab. *Dermatol Online J.* 2010;16(8):15.
23. Cariñanos I, Acosta MB, Domènech E. Adalimumab for pyoderma gangrenosum associated with inflammatory bowel disease. *Inflamm Bowel Dis.* 2011;17(12):E153-154.
24. Genevay S, Viatte S, Finckh A, Zufferey P, Balagué F, Gabay C. Adalimumab in severe and acute sciatica: a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2010;62(8):2339-2346.
25. Hoffman-La Roche. A study of efficacy and safety of tocilizumab in participants with systemic sclerosis (SSc) (focuSSced). Available from: https://clinicaltrials.gov/ct2/show/results/NCT02453256?term=tocilizumab&phase=2&rank=14. NLM Identifier: NCT02453256. Accessed June 21, 2019.
26. Mariette X, Ravaud P, Steinfeld S, et al. Inefficacy of infliximab in primary Sjögren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). *Arthritis Rheum*. 2004;50(4):1270-1276.
27. Sankar V, Brennan MT, Kok MR, et al. Etanercept in Sjögren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. *Arthritis Rheum.* 2004;50(7):2240-2245.
28. Adler S, Körner M, Förger F, Huscher D, Caversaccio MD, Villiger PM. Evaluation of histologic, serologic, and clinical changes in response to abatacept treatment of primary Sjögren's syndrome: a pilot study. *Arthritis Care Res (Hoboken).* 2013;65(11):1862-1888.
29. Meiners PM, Vissink A, Kroese FG, et al. Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). *Ann Rheum Dis.* 2014;73(7):1393-1396.
30. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med*. 2005;352(4):351-361.
31. 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.
32. 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.
33. 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.
34. 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.
35. Fujikawa K., Migita K., Tsukada T., et al. Interleukin-6 targeting therapy in familial Mediterranean Fever. Clinical and experimental rheumatology 2013:31;150-151.
36. 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.
37. 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/
38. 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.
39. Jesus AA, Goldbach-Mansky R. IL-1 Blockade in Autoinflammatory Syndromes. Annu. Rev. Med. 2014. 65:223–244.
40. Blanco FJ, Möricke R, Dokoupilova E, et al. Secukinumab in active rheumatoid arthritis: a phase iii randomized, double-blind, active comparator- and placebo-controlled study. Arthritis Rheumatol. 2017;69(6):1144-1153.
41. Tahir H, Deodhar A, Genovese M, et al. Secukinumab in active rheumatoid arthritis after anti-tnfα therapy: a randomized, double-blind placebo-controlled phase 3 study. Rheumatol Ther. 2017;4(2):475-488.
42. Dokoupilová E, Aelion J, Takeuchi T, et al. Secukinumab after anti-tumour necrosis factor-α therapy: a phase III study in active rheumatoid arthritis. Scand J Rheumatol. 2018;47(4):276-281.
43. Huang Y, Fan Y, Liu Y, Xie W, Zhang Z. Efficacy and safety of secukinumab in active rheumatoid arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta-analysis of phase III randomized controlled trials. Clin Rheumatol. 2019;38(10):2765-2776.
44. Orencia [Prescribing Information]. Bristol Myers Squibb. Princeton, NJ. December, 2021.
45. Abatacept combined with a calcineurin inhibitor and methotrexate for graft versus host disease prophylaxis: a randomized controlled trial. Results posted. Available at: https://clinicaltrials.gov/ct2/show/NCT01743131.
46. UpToDate, Inc. Psoriasis: Epidemiology, clinical manifestations, and diagnosis. UpToDate [database online]. Waltham, MA. Last updated December 30, 2019. Available at: http://www.uptodate.com/home/index.html.

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
Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Psoriatic Arthritis
	Plaque Psoriasis
	Ankylosing Spondylitis
	Non-radiographic axial spondyloarthritis (nr-axSpA)
	Crohn's Diease
	Ulcerative Colitis
	Atopic Dermatitis
Multiple Sclerosis Policy	Multiple Sclerosis
nintedanib (Ofev); prifenidone (Esbriet)	Systemic sclerosis-associated interstitial lung disease (SSc-ILD)
tapinarof (Vtama)	Plaque Psoriasis
spesolimab SC (Spevigo)	Generalized pustular psoriasis (GPP)

Policy Implementation/Update

Action and Summary of Changes	Date
Added Otezla/Otezla XR/Otezla/Otezla XR XR XR to the policy	10/2025
Updated indications table. Updated the psoriatic arthritis criteria for members 6 years or older requesting a non-preferred agent to include trial of apremilast (Otezla/Otezla XR).	08/2025
Live 07/01/2025: Stelara moved to non-preferred. Addition of select ustekinumab biosimilars (Selarsdi, Steqeyma, and Yesintek) to preferred. Moved tocilizumab-aazg (Tyenne) to first line for all applicable indications. Moved certolizumab (Cimzia) to access position, stepping through two preferred products. Revised criteria for diagnosis of GCA.	06/2025
Updated indication table format	05/2025
Broke out non preferred biosimilars to improve clarity on the requirement to trial two preferred biosimilars. Added the following language, "…biosimilar which caused patient unable to perform activities of daily living OR documentation of disease progression indicative of ineffectiveness" within multisource brand section. Addition of mirikizumab (Omvoh) in Crohn's Disease	03/2025
Removed age limits requirements. Addition of bimekizumab (Bimzelx) for the treatment of Hidradenitis Suppurativa and Psoriatic Arthritis. Addition of ustekinumab biosimilars (Steqeyma, Yesintek, Pyzchiva). Live 04/01/25: Addition of guselkumab (Tremfya) for Crohn's Disease	02/2025
Addition of ustekinumab biosimilar (Wezlana)	01/2025
Live 1/1/2025: Tyenne preferred over Actemra and moved to access position behind one preferred product.	12/2024
Removed specialist requirement in mild to moderate plaque psoriasis. Addition of certolizumab (Cimzia) to polyarticular juvenile idiopathic arthritis (pJIA). Addition of guselkumab (Tremfya) to ulcerative colitis (UC) for adults. Addition of bimekizumab (Bimzelx) to Ankylosing Spondylitis (AS) and Non-radiographic Axial Spondyloarthritis (nr-axSpA) criteria. Change to AS and nr-axSpA criteria to remove requirements for disease manifestation as axial or peripheral arthritis, change to definition of high disease activity, change to supportive evidence sections. Updated related policies.	11/2024
Removed specialist requirement in mild to moderate plaque psoriasis.	10/2024
Addition of sarilumab (Kevzara) to polyarticular juvenile idiopathic arthritis (pJIA). Removed weight requirement for Taltz in pediatric plaque psoriasis. Addition of medical necessity criteria to Entyvio SC after trial of two preferred agents in Crohn's disease and ulcerative colitis.	09/2024
Addition of risankizumab (Skyrizi) to ulcerative colitis policy requirements.	08/2024
Addition of vedolizumab SC (Entyvio) to Crohn's disease policy requirements. Otezla/Otezla XR age expansion in the setting of moderate to severe plaque psoriasis.	07/2024
Addition of tocilizumab-aazg (Tyenne) into policy	06/2024
Addition of bimekizumab (Bimzelx) into policy.	03/2024
Live 04/01/2024: addition of select biosimilars (Hadlima and adalimumab-adaz) as preferred products, removal of brand Humira as a preferred product.	02/2024

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	
Added age expansions for abatacept (Orencia) and etanercept (Enbrel) in psoriatic arthritis. Added etrasimod (Velsipity) to ulcerative colitis policy. Added infliximab-dyyb (Zymfentra) as not medically necessary to ulcerative colitis and Crohn's Disease criteria. Updated Supportive evidence section and not medically necessary sections.	01/2024
Live 01/2024: Added guselkumab (Tremfya) as a preferred product.	11/2023
Added vedolizumab SC (Entyvio) to policy for ulcerative colitis as not medically necessary when used for all indications. Updated Investigational or Not Medically Necessary Uses section to include vedolizumab SC (Entyvio). Added mirikizumab (Omvoh) to policy for ulcerative colitis indication. Updated supportive evidence section accordingly.	11/2023
Added criteria for anakinra (Kineret) off-label use in TRAPS (tumor necrosis factor receptor-associated periodic syndrome), FMF (Familial Mediterranean Fever) and HIDS/MKD (hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency). Removed FMF (Familial Mediterranean Fever) from the E/I section.	10/2023
Addition of new adalimumab biosimilars into policy.	07/2023
Live 12/2023: Updated criteria for hidradenitis suppurativa to include new line indication for Cosentyx. Updated supporting evidence and references.	06/2023
Added polymyalgia rheumatica indication for Sarilumab (Kevzara) with associated criteria and supporting evidence. Removed polymyalgia rheumatica from E/I section.	06/2023
Live 06/2023: Added Rinvoq to Crohn's Disease policy, updated supportive evidence section for Crohn's Disease, updated references for Crohn's Disease, updated Related Policies section. Removed step criteria requiring trial of corticosteroids in giant cell arteritis. Added updated supporting evidence and updated guideline recommendations.	03/2023
Addition of adalimumab-atto (Amjevita) into policy.	02/2023
Updated nr-axSpA formulary agents to include new line indication for Rinvoq. Updated supporting evidence and references for AS and nr-axSpA. Updated wording of renewal criteria regarding combination biologic use to reflect specific disease state referenced. Updated related policies section.	11/2022
Added Stelara age expansion in psoriatic arthritis to include members 6 years of age or older, formatting, and supporting evidence.	10/2022
Added Skyrizi to Crohn's disease criteria, updated supporting evidence section, updated formatting. Updated AS formulary agents to include new indication for Rinvoq.	06/2022
Added Rinvoq to ulcerative colitis criteria given newly approved indication	05/2022
Updated criteria in setting of mild-moderate plaque psoriasis to require phototherapy OR treatment with only one of the list groups	04/2022
Added ERA section and created criteria for use of Cosentyx as prompted by recent FDA approval. Updated PsA criteria to include expanded age for Cosentyx and new FDA approval for Skyrizi. Refined supporting evidence for PJIA and PsA to further clarify guidelines and treatment algorithm in pediatrics.	03/2022
Added criteria for Otezla/Otezla XR to include line extension in setting of mild to moderate psoriasis with update to supporting evidence section. Updated PsA and AS formulary agents to include new indications for Rinvoq and Xeljanz with updates to supporting evidence and references. Removed Behcet's oral corticosteroid requirement and updated to include systemic therapy to align more appropriately with guidelines. Updated Palmoplantar pustulosis E/I summary. Added Graft Vs. Host disease to E/I.	2/2022
Added Skyrizi, Rinvoq, and Xeljanz to the preferred product mix (effective 1/1/2022). Separated/removed JAK inhibitors (Xeljanz, Rinvoq, Olumiant) and created JAK Inhibitor Policy. Removed JAK inhibitors in E/I section and added Cosentyx in RA to E/I. Added Related Policies section.	12/2021
Removed criteria defining moderate to severe Crohn's disease, severe/fulminant Crohn's disease, and surgical Crohn's disease. Updated supporting evidence section accordingly.	09/2021
Added criteria for the treatment of systemic sclerosis-associated interstitial lung disease prompted by new FDA approval of Actemra for this indication.	08/2021
Updated Plaque Psoriasis, Cosentyx criteria to allow coverage in patients 6 six years of age or older	07/2021
Added criteria for treatment of recurrent pericarditis with Arcalyst	06/2021
Updated criteria for ulcerative colitis to include FDA approval of ozanimod (Zeposia) for adults with moderate to severe ulcerative colitis. Modified 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 criteria for ulcerative colitis to include FDA approval of adalimumab (Humira) for pediatric patients five years and older. Added the requirement for the documentation of member's current weight. Updated the language in the criterion requiring use of thiopurines only if corticosteroids were used to induce remission. Supporting evidence and references updated.	05/2021
Added DIRA indication as E/I for anakinra (Kineret); Updated the supporting evidence and references for plaque psoriasis.	04/2021
Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data	11/2020
Updated PA policy to include FDA approvals for Stelara and Taltz for plaque psoriasis in pediatric population. Updated supporting information section for plaque psoriasis to include clinical trial data supporting use of Stelara and Taltz in pediatric patients	09/2020
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). Updated non-radiographic axial spondyloarthritis (nr-axSpA) criteria to include secukinumab (Cosentyx) and ixekizumab (Taltz). Updated nr-axSpA supporting evidence section to include trial information regarding new addition of secukinumab (Cosentyx) and ixekizumab (Taltz), as well as updated ACR guidelines.	08/2020
Removed Behçet syndrome from the E/I section	02/2020
Updated preferred products to also include Cosentyx, Stelara, and Otezla/Otezla XR within their FDA label designation.	01/2020
Updated policy to add new indications for Stelara and Taltz. Included Familial Mediterranean Fever to experimental/investigational section.	11/2019
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>Systemic Juvenile Idiopathic Arthritis (SJIA)</u> • Separated SJIA from PJIA to have individual requirements • Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement • Updated route to approval to require trial of NSAIDs or indication member has severe active disease • Routed therapy through anakinra (Kineret) over tocilizumab (Actemra) and abatacept (Orencia); followed by tocilizumab (Actemra) over abatacept (Orencia) as per <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>Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis</u> • Removal of the requirement of DMARDs per the 2015 ACR guideline and 2016 ASAS/EULAR guideline • Added requirement of a trial of two or more NSAIDS for an adequate trial of at least 4 weeks, also based on the above guidelines <u>Plaque Psoriasis</u> • Clarified that moderate to severe disease is needed for payment consideration • Clarified use of oral DMARD requirement may be bypassed if all are contraindicated	08/2019

Crohn's Disease
• Added age requirement of six years of age or older
• Incorporated definition of moderate to severe Crohn's disease to help confirm disease severity
• Addition of breakdown to separate severe/fulminant Crohn's disease with definition to help confirm disease severity
  ○ Addition of IV corticosteroids as appropriate for this level of severity
• Addition of breakdown to Crohn's disease with surgical resection completed or planned
  ○ With further addition requiring presence of one additional factor demonstrating medical necessity of biologic treatment
Ulcerative Colitis
• Added age of 18 years or older
• Addition of trial of thiopurine for at least 8 weeks
Behcet's Disease
• New indication added following approval of Otezla/Otezla XR in this setting
• Literature supports TNF therapy in oral and ophthalmic manifestations for Behcet's. A path to approval was added to the criteria
• Otezla/Otezla XR was added as a potential option after TNF have been found inefficacious or are contraindicated
Hidradentitis Suppurativa
• Updated prescriber language to be consistent with other sections
• Added requirement of a trial of antibiotics for moderate disease
Uveitis/Panuveitis
• Added age of 2 years or older
• Improved trial/fail wording to state "ineffective, contraindicated, or not tolerated"
  ○ No changes to trial and failure requirements
Giant Cell Arteritis (GCA)
• Added age of 18 years or older
• Added criteria endorsed by guidelines to confirm diagnosis of GCA
• Updated terminology around steroid use to require a previous trial with steroids rather than requiring concomitant steroid use with Actemra
Cryopyrin-Associated Periodic Syndromes (CAPS)
Added requirement, of documented laboratory evidence of a genetic mutation	

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
Criteria update: Align dosage and administration with quantity limit. Removal of the question pertaining to active infection.	02/2018
New Criteria Set – consolidated from all biologic agents along with Otezla/Otezla XR 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 3. The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla/Otezla XR 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.	01/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP070

Description

Cobimetinib (Cotellic) is an orally administered mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2 inhibitor. Vemurafenib (Zelboraf) is an orally administered BRAF kinase inhibitor. These agents are FDA-approved for combination use or single use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	20 mg tablets	63 tablets/28 days
	Histiocytic neoplasms in adults		
vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation	240 mg tablets	224 tablets/28 days
	Erdheim-Chester disease with a BRAF V600 mutation		

Initial Evaluation

I. **Cobimetinib (Cotellic) and vemurafenib (Zelboraf**) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medications are prescribed by, or in consultation with, an oncologist; **AND**
   C. A diagnosis of one of the following:
      1. **Unresectable, locally advanced (Stage IIIC) or metastatic (Stage IV) melanoma; AND**
         i. Documented BRAF V600E or V600K mutation; **AND**
         ii. Member has not previously received systemic anti-cancer therapy for metastatic melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy); **AND**
         iii. Cobimetinib (Cotellic) will be used only in combination with the following:

a. Vemurafenib (Zelboraf); **OR**
b. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq); **OR**

2. **Histiocytic Neoplasms (i.e., Erdheim-Chester disease, Rosai-Dorfman disease, Langerhans cell histiocytosis); AND**
   i. Documentation of prior treatment with, intolerance, or contraindication to both of the following:
      a. Cytarabine (non Erdheim-Chester disease indications)
      b. Cladribine; **AND**
   ii. Provider attestation member is not eligible or does not have access to clinical trial; **AND**
   iii. The request is for cobimetinib (Cotellic) monotherapy; **AND**
      a. Member has not previously progressed on therapy with a MEK inhibitor [i.e, binimetinib (Mektovi), selumetinib (Koselugo), or trametinib (Mekinist)];**AND**
      b. Member has had previous progression on or after BRAF inhibitor [e.g., vemurafenib (Zelboraf)]; **AND**
         i. Provider attestation that the member has an amenable MEK mutation; **OR**
   iv. The request is for vemurafenib (Zelboraf) monotherapy; **AND**
      a. Member has a diagnosis of Erdheim-Chester disease; **AND**
      b. Documented BRAF V600E mutation.

II. Cobimetinib (Cotellic) and vemurafenib (Zelboraf) are considered investigational when used for all other conditions, including but not limited to:
   A. Wild-type BRAF melanoma
   B. Melanoma in the neoadjuvant setting
   C. Breast cancer, solid tumors, colorectal cancer, thyroid cancer, central nervous system cancer, follicular/papillary cancer, and non-small cell lung cancer (NSCLC) with/without BRAF V600E mutation
   D. Hairy cell leukemia
   E. Cotellic in combination with Zelboraf for treatment of histiocytic neoplasms

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 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 stabilization of disease or decrease in tumor size or tumor spread; **AND**
   A. **For treatment of melanoma:** the request is for cobimetinib (Cotellic) to be used only in combination with the following:

1. Vemurafenib (Zelboraf); **OR**
2. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq); **OR**

B. **For the treatment of histiocytic neoplasms; AND**
   a. The request is for cobimetinib (Cotellic) monotherapy; **OR**
   b. The request is for vemurafenib (Zelboraf) monotherapy; **AND**
      i. Member has a diagnosis of Erdheim-Chester disease**.**

Supporting Evidence

I. **Advanced or Metastatic Melanoma**
   A. Cobimetinib (Cotellic) is indicated for use in two different combinations for patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.
      i. In combination with vemurafenib (Zelboraf)– coBRIM trial
      ii. In combination with atezolizumab (Tecentriq) and vemurafenib (Zelboraf)– IMspire150 trial
   B. Cobimetinib (Cotellic) was studied in a phase 3, randomized, double-blind, placebo-controlled trial (coBRIM) in 495 patients with unresectable, locally advanced stage IIIC or IV BRAF-mutated melanoma. The trial evaluated treatment with cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) (COBI-VEM) compared to placebo with vemurafenib (Zelboraf) (PBO-VEM). The trial studied patients who were treatment-naïve defined as no prior systemic advanced/metastatic melanoma therapy (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, and biologic therapy), but did allow prior adjuvant therapy (including immunotherapy, e.g., ipilimumab).
      i. The primary endpoint was progression free survival (PFS), which resulted in 9.9 months in the COBI-VEM arm compared to 6.2 months in the PBO-VEM arm. Additionally, updated results, approximately 14 months post-trial, concluded PFS of 12.3 months in the COBI-VEM arm compared to 7.2 months in the PBO-VEM arm. Key secondary endpoints were overall survival (OS), which was 22.3 months in the COBI-VEM arm compared to 17.4 months in the PBO-VEM arm; complete response rate (CRR) of 68% in the COBI-VEM arm compared to 45% in the PBO-VEM arm; and duration of response (DoR) of 13 months in the COBI-VEM arm compared to 9.2 months in the PBO-VEM arm. Quality of life (QoL) parameters were studied; however, QoL analysis was not performed in all patients and was not studied through the entire length of the trial. QoL was evaluated until cycle 8 day 1, after which investigators report less than 25% of patients with baseline QoL scores remained enrolled in the PBO arm. There were no differences in quality-of-life scores between the two groups.
      ii. Safety results were analyzed in all patients who received at least one dose of study drug (N=254 COBI-VEM, N=239 PBO-VEM). The most common adverse events (>20% incidence) included diarrhea, nausea, vomiting, rash, photosensitivity reaction, hyperkeratosis, fatigue, pyrexia, arthralgia, alopecia, and increase creatine kinase. Cobimetinib (Cotellic) showed a 55%

discontinuation rate: 14% due to adverse events versus 7% in the PBO-VEM arm.

C. Cobimetinib (Cotellic) was also studied in a phase 3, randomized, double-blind, placebo-controlled trial (IMspire150) in 514 patients with unresectable, locally advanced stage IIIC or IV BRAF-mutated melanoma. The trial evaluated treatment with atezolizumab (Tecentriq) in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf) (ATEZO-COBI-VEM) compared to placebo, cobimetinib (Cotellic), and vemurafenib (Zelboraf) (PBO-COBI-VEM). The trial studied patients who were treatment-naïve defined as no prior systemic melanoma therapy (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies); however, use with prior adjuvant therapy was allowed.
    i. The primary endpoint was PFS, which resulted in 15.1 months in the ATEZO-COBI-VEM arm compared to 10.6 months in the PBO-COBI-VEM arm. Key secondary endpoints were OS, which was 28.8 months versus 25.1 months in the PBO-COBI-VEM arm (HR 0.85, 95% CI 0.64-1.11, p=0.231); objective response rate (ORR), which was 66.3% versus 65% in the PBO-COBI-VEM arm; and DoR, which was 21 months versus 12.6 months in the PBO-COBI-VEM arm. QoL parameters were studied, which was 14.4 months to decline in QoL in the ATEZO-COBI-VEM arm, and not estimable for the comparator (HR 1.23, 95% CI 0.9-1.67).
    ii. Safety results were analyzed in all patients who received at least one dose of study drug (N=230 ATEZO-COBI-VEM, N=281 PBO-COBI-VEM). The most common adverse events (>20% incidence) included increased blood creatine phosphokinase, rash, diarrhea, arthralgia, pyrexia, increased alanine aminotransferase aspartate, increased lipase, increased aminotransferase, fatigue, nausea, pruritus, myalgia, photosensitivity, maculopapular rash, and increase amylase. Overall, 44% discontinued treatment in the ATEZO-COBI-VEM arm compared to 51% in the PBO-COBI-VEM arm: 13% in the ATEZO-COBI-VEM arm due to adverse events versus 16% in the PBO-COBI-VEM arm.

D. As of January 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for cutaneous melanoma has included cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) as first-line therapy (Category 1) or subsequent systemic therapy (Category 2A) for metastatic or unresectable disease. Additionally, triple therapy of atezolizumab (Tecentriq) in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf) were included as first-line therapy with a Category 2A recommendation.

II. **Histiocytic Neoplasms**

A. Histiocytic neoplasms are a heterogeneous group of clonal hematopoietic disorders thought to be derived from mononuclear phagocytic cells (macrophages and dendritic cells) or histiocytes. The Histiocyte Society's classification divides histiocytic disorders into five categories, based on clinical, histologic, immunophenotypic, and molecular features. Its Langerhans group includes LCH, Erdheim-Chester disease (ECD), mixed LCH/ECD, indeterminate cell histiocytosis, and extracutaneous juvenile xanthogranuloma.

B. Histiocytic neoplasms are heterogeneous, and presentation varies from localized and mild to disseminated and lethal. Initial presentation is often nonspecific but is marked by diverse mutations in the mitogen-activated protein kinase (MAPK) pathway. ERK dependence has been hypothesized to be a consistent feature across the group.
C. The evidence supporting the management of histiocytic neoplasms in adults is largely based on small retrospective studies, case series, and case reports, due to the rarity of prospective studies in adults. In addition, some of the diagnostic and treatment recommendations for adults with histiocytic neoplasms are, of necessity, extrapolated from prospective studies in children and young adults, except when stated otherwise. NCCN guidelines focus recommendations onto three of the histiocytic neoplasms: LCH, ECD, and RDD.
D. Current treatment options for LCH, ECD, and other histiocytic neoplasms include targeted therapies (BRAF: vemurafenib, PIK3CA/ALK/MAP2K1/etc: cobimetinib, trametinib, dabrafenib, ALK inhibitors), interferon alfa, glucocorticoids, methotrexate, mTOR inhibitors, systemic chemotherapy, and clinical trials. NCCN guidelines recommend first or subsequent-line therapy with vemurafenib (BRAF V600 mutation), cobimetinib (MAPK mutation or no mutation) or treatments irrespective of mutation cladribine, cytarabine (non-ECD histiocytic neoplasms), interferon alpha (ECD); other recommended regimens target identified mutations.
E. Cobimetinib (Cotellic) is FDA approved as a single agent for the treatment of adult patients with histiocytic neoplasms. Cobimetinib (Cotellic) was studied in a phase 2, single arm, open-label trial of patients with histologically confirmed histiocytic disorders. Participants (n=26) included those diagnosed with Langerhans Cell Histiocytosis (n=4), Rosai-Dorfman Disease (n=4), Erdheim-Chester Disease (n=13), Xanthogranuloma (n=2) and Mixed Histiocytosis (n=3). Of the 26 participants 6 were BRAF V600 mutant positive and 20 were BRAF V600 wild type. Those with documented BRAF V600E mutations were enrolled if they were unable to access a BRAF inhibitor or if they discontinued a BRAF inhibitor due to toxicity. Additionally, those BRAF mutated patients had to have subsequent testing to assess for amenable mutations. Other baseline characteristics included: median age 50.5 years (range, 18 to 79 years), male (65%), White (85%), Black or African American (8%), and Asian (4%). Those with prior history of therapy with MEK inhibitors [i.e, binimetinib (Mektovi), selumetinib (Koselugo), or trametinib (Mekinist)] were excluded. The primary endpoint was overall response rate (measured via PET response), which was obtained in 76.9% of participants (95% CI 56.4 – 91). The overall level of evidence is considered low given the lack of a comparator arm and overall survival data; however, given the limited options in this disease state, allowance for coverage has been outlined in the criteria section above.
F. Vemurafenib (Zelboraf) was studied in one single-arm, open-label, and multiple cohort basket trial of patients with non-melanoma BRAF V600 mutation-positive disease (n=26), including 22 patients with ECD and four with Langerhans Cell Histiocytosis, a similar but distinctly different type of histiocytic neoplasm. Population characteristics were as follows: median age 58.5 years (range 34-77 years), 55% male, 68% previous systemic therapy. Primary endpoint was overall response rate, which was obtained in 54% of participants (95% CI 32.2 – 75.6). Given the study design, and the inability to

distinguish between the effect of vemurafenib (Zelboraf) and the natural history of ECD, the evidence is considered low quality; however, given the limited options in this disease state, allowance for coverage has been outlined in the criteria section above.

G. Combination therapy with cobimetinib (Cotellic) and vemurafenib (Zelboraf) has not been evaluated for use in histiocytic neoplasms.

Investigational or Not Medically Necessary Uses

I. Cobimetinib (Cotellic) has not been sufficiently evaluated outside of unresectable or metastatic melanoma and histiocytic neoplasms. Limited evidence is available consisting of early phase studies evaluating use in other cancers; however, safety and efficacy have not been established in these conditions:
   A. Wild-type BRAF melanoma
   B. Melanoma in the neoadjuvant setting
   C. Breast cancer, solid tumors, colorectal cancer, thyroid cancer, central nervous system cancer, follicular/papillary cancer and non-small cell lung cancer (NSCLC) with/without BRAF V600E mutation
   D. Hairy cell leukemia
   E. Cotellic in combination with Zelboraf for histiocytic neoplasms

References

1. Cotellic [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated October 2022. Accessed February 2023.
2. Tecentriq [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated December 2020. Accessed January 2021.
3. Zelboraf [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated May 2020. Accessed June 2022.
4. National Comprehensive Cancer Network NCCN Guidelines: Melanoma: Cutaneous v1.2021. November 25, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed January 2021.
5. Larkin J, Ascierto PA, Dreno B et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med* 2014;371(2):1867-1876. Available at: https://pubmed.ncbi.nlm.nih.gov/25265494/
6. Ascierto PA, McArthur GA, Dreno B et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016;17:1248-1260. Available at: https://pubmed.ncbi.nlm.nih.gov/27480103/
7. Gutzmer R, Stroyakovskiy D, Gogas H et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;395:1835-1844. Available at: https://pubmed.ncbi.nlm.nih.gov/32534646/
8. National Comprehensive Cancer Network NCCN Guidelines: Histiocytic Neoplasms v1.2022. May 20, 2022. Available at https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf. Accessed February 2022.
9. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature. 2019;567(7749):521-524.

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
trametinib (Mekinist®), dabrafenib (Tafinlar®)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy
	Melanoma, BRAF V600E or K mutated, adjuvant therapy for malignant disease as combination therapy and for malignant unresectable or metastatic disease as monotherapy in treatment-naïve patients
	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
selumetinib (Koselugo™)	Neurofibromatosis type 1 (NF1)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication for cobimetinib (Cotellic) in histiocytic neoplasms with supporting evidence. Combined initial criteria and renewal criteria sections to include ECD under histiocyctic neoplasms. Updated E/I section to disallow combination use of cobimetinib (Cotellic) and vemurafenib (Zelboraf) for histiocytic neoplasms. Removed RDD and LCH from E/I. Updated related policies criteria to include selumetinib (Koselugo).	06/2023
Revised initial and renewal criteria to align standard verbiage/formatting. Removed requirement for oncologist prescriber/consultation in renewal criteria. Updated supporting evidence for Erdheim-Chester disease. Added cobimetinib (Cotellic) monotherapy or combination with vemurafenib (Zelboraf) for ECD to E/I section with supporting evidence. Added Related Policies table.	06/2022
Cobimetinib (Cotellic) criteria transitioned to policy format. Consolidated cobimetinib (Cotellic) and vemurafenib (Zelboraf) criteria. Addition of E/I and supporting evidence section. Updated length of initial approval from three to six months. Addition of the following to initial criteria: age requirement (18+yrs); not to be used in combination with any other oncology therapy unless outlined in criteria; disease is unresectable/locally advanced (Stage IIIC) or metastatic (Stage IV); provider attestation to all the following: member has not previously received systemic anti-cancer therapy for melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy), or if previously received immunotherapy, treatment was for use in the adjuvant setting only; additional combination agent option (atezolizumab [Tecentriq] and vemurafenib [Zelboraf]). Addition of the following to renewal criteria: member has received a previous prior authorization approval for this agent through this health; 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; medication prescribed by, or in consultation with, an oncologist; not to be used in combination with any other oncology therapy unless outlined in criteria. In consolidation, removed verbiage requiring BRAF V600E mutation "by an FDA-approved test" from vemurafenib (Zelboraf) criteria. Updated QL for vemurafenib (Zelboraf) to align with cobimetinib (Cotellic), from 240 tablets per 30 days to 224 tablets per 28 days.	01/2021
Policy created	02/2016

colchicine (Lodoco®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP286

Description

Colchicine (Lodoco) is an orally administered alkaloid. The mechanism of action of colchicine (Lodoco) in prevention of major cardiovascular events is not well understood at this time.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
colchicine (Lodoco)	Cardiovascular risk reduction in patients with established atherosclerotic cardiovascular disease (ASCVD) or with multiple risk factors for cardiovascular disease	0.5mg tablet	30 tablets/30 days

Initial Evaluation

I. **Colchicine (Lodoco)** may be considered medically necessary when the following criteria are met:
   A. Member is 35 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a provider specializing in heart disease (i.e., cardiology, lipidology); **AND**
   C. A diagnosis of **established Atherosclerotic Cardiovascular Disease (ASCVD)** when the following are met:
      1. Diagnosis is confirmed by one of the following:
         i. Primary prevention failure (e.g., member has had a stroke, myocardial infarction, percutaneous coronary intervention [PCI], etc.); **OR**
         ii. Evidence of clinical atherosclerotic disease on invasive or non-invasive testing (e.g., coronary angiography, CT angiography, etc.); **AND**
      2. Blood pressure is controlled and stable on current antihypertensive therapy; **AND**
      3. Provider attestation that member does not have any of the following comorbidities:
         i. Renal failure (i.e., CrCl <15 mL/min)
         ii. Severe liver impairment
         iii. Pre-existing blood dyscrasias
         iv. Concurrent use of strong CYP3A4 or P-gp inhibitors; **AND**
      4. Member will continue background therapy with maximally tolerated statin (e.g., atorvastatin, rosuvastatin, simvastatin, etc.); **OR**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ArrayRx administered by moda HEALTH

i. If statin intolerant, member will continue background therapy with maximally tolerated non-statin lipid-lowering agents (e.g., ezetimibe, Repatha, Praluent, fenofibric acid, etc.) unless contraindicated or not tolerated; **AND**

5. Treatment with colchicine 0.6mg (Colcrys) has been ineffective, contraindicated, or not tolerated

II. Colchicine (Lodoco) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Gout
   B. Familial Mediterranean fever

III. Colchicine (Lodoco) is considered investigational when used for all other conditions, including but not limited to:
   A. Actinic Keratosis
   B. Amyloidosis
   C. Behcet's syndrome
   D. Pericarditis, acute or recurrent
   E. Post-pericardiotomy 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. Member has not experienced a major cardiovascular event (e.g., stroke, myocardial infarction); **OR**
   - If member has experienced a major cardiovascular event, 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; **AND**

IV. Member will continue background therapy with maximally tolerated statin (e.g., atorvastatin, rosuvastatin, simvastatin, etc.); **OR**
   - If statin intolerant, member will continue background therapy with maximally tolerated non-statin lipid-lowering agents (e.g., ezetimibe, Repatha, Praluent, fenofibric acid, etc.) unless contraindicated or not tolerated; **AND**

V. Treatment with colchicine 0.6mg (Colcrys) has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. Colchicine (Lodoco) 0.5mg tablets was evaluated in one pivotal phase 3, randomized, double-blind, placebo-controlled trial (LoDoCo2) to evaluate the safety and efficacy in patients with chronic coronary artery disease in 5,522 adult patients aged 35 to 82 years old. The primary

composite endpoint of time to first cardiovascular (CV) death, spontaneous (non-procedural) myocardial infarction (MI), ischemic stroke, or ischemia-driven coronary revascularization was statistically significant compared to placebo, with an incidence rate per 100 person-years of 2.5 and 3.6 events, respectively [(hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001)]. The key secondary endpoint of composite of CV death, spontaneous MI, or ischemic stroke was also met, with incidence rates of 1.5 and 2.1 events per 100 person-years in the colchicine and placebo groups, respectively [hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P = 0.007)].

II. The most commonly adverse event reported during the LoDoCo2 clinical trial was myalgia, which occurred in 21.2% of colchicine (Lodoco) treated patients and 18.5% of patients in the placebo group. Colchicine (Lodoco) also carries labeled contraindications for use in patients with renal failure (e.g., CrCl <15 mL/min), severe hepatic impairment, and pre-existing blood dyscrasias due to higher risk of toxicity in this population.

III. 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. The inclusion trial for the LoDoCo2 clinical trial also included patients who had proven coronary disease by a Coronary Artery Calcium score ≥400; Although coronary calcium scores are not typically used as a diagnostic tool for ASCVD, this could be accepted as a verification of ASCVD based on the population colchicine (Lodoco) was studied in.

IV. Emerging data has shown that inflammation, in addition to hyperlipidemia, contributes to the risk of future atherothrombotic events. A collaborative analysis of three randomized trials observed that inflammation of high-sensitivity C-reactive protein (CRP) was a stronger predictor for risk of future CV events and death than cholesterol assessed by low-density lipoprotein cholesterol (LDL-C). The 2021 ESC guidelines for secondary prevention of CV events indicates that colchicine is an appropriate therapy to consider in patients with established ASCVD (secondary prevention) who remain at very high risk of future CV events, particularly if other risk factors are insufficiently controlled or if recurrent CV events occur under optimal therapy (i.e., controlled blood pressure, controlled hyperlipidemia, etc.). Guidelines indicate that statins continue to provide the strongest level LDLC reduction and protection against CV events; however, in those who do not tolerate statin therapy, use of other anti-hyperlipidemic therapy is appropriate to reduce LDL.

V. Although colchicine 0.6mg tablet has not specifically been studied in the setting of CV prevention, this is likely due to the lack of availability of this formulation in the geography of the clinical trial (i.e., Europe). There is no anticipated clinically meaningful difference in the effect of colchicine 0.5mg (Lodoco) compared to 0.6mg; therefore, the off-label use of colchicine 0.6mg tablets is required as cost-effective step therapy.

Investigational or Not Medically Necessary Uses

I. Colchicine (Lodoco) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Gout
      i. Colchicine 0.6mg (Colcrys) is currently FDA-approved for the treatment of gout. Although there is no anticipated clinically meaningful difference in the effect of

colchicine 0.5mg (Lodoco) compared to 0.6mg, therapies are only considered medically necessary when prescription drug or prescription drug dose recommended for this condition is cost-effective compared to alternative interventions, including no intervention. Since colchicine 0.6mg tablets are considered a cost-effective therapy, use of colchicine 0.5mg (Lodoco) is considered not medically necessary for this indication.

B. Familial Mediterranean fever
    i. Colchicine 0.6mg (Colcrys) is currently FDA-approved for the treatment of familial mediterranean fever. Although there is no anticipated clinically meaningful difference in the effect of colchicine 0.5mg (Lodoco) compared to 0.6mg, therapies are only considered medically necessary when prescription drug or prescription drug dose recommended for this condition is cost-effective compared to alternative interventions, including no intervention. Since colchicine 0.6mg tablets are considered a cost-effective therapy, use of colchicine 0.5mg (Lodoco) is considered not medically necessary for this indication.
C. Actinic Keratosis
D. Amyloidosis
E. Behcet's syndrome
F. Pericarditis, acute or recurrent
G. Post-pericardiotomy syndrome

Appendix

I. Table 1: Examples of CYP3A4 and P-gp inhibitors

Strong CYP3A4 inhibitors	Atazanavir
	Clarithromycin
	Darunavir/ritonavir
	Indinavir
	Itraconazole
	Ketoconazole
	Lopinavir/ritonavir
	Nefazodone
	Nelfinavir
	Ritonavir
	Saquinavir
	Telithromycin
	Tipranavir/ritonavir
Moderate CYP3A4 inhibitors	Amprenavir
	Aprepitant
	Diltiazem
	Erythromycin
	Fluconazole
	Fosamprenavir (prodrug of amprenavir)
	Verapamil

P-gp inhibitors	Cyclosporine
	Ranolazine

References

1. LODOCO. Package inset. Agepha Pharma USA, LLC; June 2023.
2. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383(19):1838-1847. doi:10.1056/NEJMoa2021372
3. Ridker PM, Bhatt DL, Pradhan AD, et al. Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomized trials. *Lancet* 2023; 401: 1293-301.
4. IPD Analytics. RX Insights: Cardiovascular – Lodoco for Cardiovascular Risk Reduction. Published July 2023.
5. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. European Heart Journal (2021); 42, 3227-3337.
6. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation*. 2019; 140: e596-e646.

Related Policies

Policy Name	Disease state
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor Policy	Atherosclerotic cardiovascular disease (ASCVD)
Bempedoic acid, bempedoic acid/ezetimibe (Nexletol™, Nexlizet™)	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with established atherosclerotic cardiovascular disease who require additional lowering of LDL-C

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	09/2023

concizumab (Alhemo®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP320

Description

Concinzumab (Alhemo) is a subcutaneous tissue factor pathway inhibitor (TFPI) antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
concinzumab (Alhemo)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with Hemophilia A or Hemophilia B with factor inhibitors	60 mg/1.5 mL (40 mg/mL) prefilled pen 150 mg/1.5 mL (100 mg/mL) prefilled pen 300 mg/3 mL (100 mg/mL) prefilled pen	**Initial:** Loading: 1mg/kg/day (round up to the nearest package size) Maintenance: 0.2mg/kg/day (round up to the nearest package size) **Renewal:** Dose calculated on the basis of plasma level (round up to the nearest package size) • Less than 200 ng/mL: 0.25 mg/kg/day • 200 to 4,000 ng/mL: 0.2 mg/kg/day • Greater than 4,000 ng/mL: 0.15 mg/kg/day

Initial Evaluation

I. **Concinzumab (Alhemo)** 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 hematologist; **AND**
   C. Medication will not be used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
   D. Concinzumab (Alhemo) will be used as routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
   E. Clinical documentation confirming that the member has a history of inhibitors [i.e., documented high-titer inhibitor (>5 BU/mL)]; **AND**
   F. Documentation of the member's weight; **AND**
   G. A diagnosis of one of the following:
      1. **Hemophilia A**; **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

i. Member has had two or more documented episodes of spontaneous bleeding; **AND**
ii. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**

2. **Hemophilia B**; **AND**
   i. Member has had two or more documented episodes of spontaneous bleeding; **OR**
      a. Member has had an inadequate response to Immune Tolerance Induction (ITI)

II. Concizumab (Alhemo) is considered investigational when used for all other conditions, including but not limited to:
   A. Concizumab (Alhemo) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
   B. Pediatric patients <12 years of age with hemophilia A or B
   C. Hemophilia A without inhibitors
   D. Hemophilia B without inhibitors
   E. Von Willebrand 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 (e.g., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**
IV. Medication will not be used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
V. Documentation of member's weight; **AND**
VI. Documentation of member's concizumab (Alhemo) plasma concentration; **AND**
VII. If the previous plasma concentration was under 200 ng/mL, there is now documentation member's concizumab (Alhemo) plasma concentration is greater than or equal to 200 ng/mL

Supporting Evidence

I. Concizumab (Alhemo) is a tissue factor pathway inhibitor (TFPI) antagonist FDA-approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with hemophilia A and B with inhibitors. Tissue factor pathway inhibitor (TFPI) is an anticoagulation protein that regulates the extrinsic coagulation cascade by inactivating the protease functions of FXa/FVIIa/TF complex. When TFPI activity is blocked, the extrinsic coagulation cascade continues to work without requiring amplification by FVIII/FIX whose normal plasma levels are reduced in hemophilia.

II. The efficacy and safety of concizumab (Alhemo) has not been studied in a pediatric population less than 12 years of age. Current FDA approval is limited to those 12 years of age and older.

III. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX) are X-linked inherited coagulation factor deficiencies that result in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A and B. The severity of an individual's hemophilia is determined by the amount of clotting factor present. Plasma levels of FVIII or FIX < 40% are indicative of hemophilia; however, hemophilia A and B are classified moderate when factor levels are 1% to < 5%, and severe when factor levels are < 1%. Joint bleeds are the most frequent bleeding experienced by people with hemophilia of all severities (70-80%) which can lead to deformity, arthropathy, and irreversible joint damage leading to decreased mobility. Given the complexities of diagnosis and treatment of hemophilia A and B, supervision of treatment by a hematologist is required.

IV. Typical hemophilia therapies include factor replacement with clotting factor concentrates (CFCs). For some patients treated with CFCs, neutralizing antibodies (i.e., inhibitors) develop in response to repeated exposure to exogenous factor products. Inhibitors are most commonly developed in patients with severe hemophilia A (30%). Incidence of inhibitor development in mild and moderate hemophilia A and hemophilia B populations are lower at 5% and 3% respectively. Inhibitors can significantly increase the cost of care and make bleeding episodes more difficult to treat as high doses of CFCs or bypassing agents are needed to circumvent inhibitors.

V. The World Federation of Hemophilia (WFH) guidelines recommend use of agents for both bleeding prophylaxis and control of acute breakthrough bleeds. Therapy recommendations are not sequential but rather cite the need for individualized care considering a patient's bleeding phenotype, joint status, pharmacokinetic profile, and preference. Medications include factor replacement with clotting factor concentrates (CFCs) (i.e., standard half-life (SHLs) for FVIII for hemophilia A and FIX for hemophilia B), long-acting CFCs (i.e., extended half-life (EHLs)), non-factor, and gene therapies. The frequency of injections varies but overall injection burden is high. The WFH split treatment recommendations for hemophilia A with inhibitors (HAwI) and hemophilia B with inhibitors (HBwI) based on whether the inhibitor is low-responding or high-responding. The WFH recommends FVIII concentrate for hemophilia A patients with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate) for those with high-responding inhibitors. Hemophilia B patients with low-responding FIX inhibitors, use of a FIX-containing product to treat acute bleeds is recommended. Whereas for those with high-responding FIX inhibitors, rFVIIa is preferred. Additionally, HAwI and HBwI patients may undergo immune tolerance induction (ITI) to eradicate the inhibitor and, thus, allow the patient to return to ordinary CFC replacement therapies. The basic approach used by ITI is to give large doses of FVIII for FIX, often daily, for months or years. The relative success rate of ITI can be low and is only guideline recommended for HAwI though it can be used in HBwI. For patients with hemophilia A who develop persistent low responding inhibitors, the WFH suggests that immune tolerance induction ITI be considered. Guidelines have not been updated to include concizumab (Alhemo).

VI. There are varying severities of hemophilia A and B depending on the level of factor produced by the patient, these are divided into the following per the International Society on Thrombosis and Hemostasis (ISTH):

- Severe: <1% factor activity (<0.01 IU/mL)
- Moderate: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)

- Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)

VII. There is a lack of strong scientific evidence from randomized controlled trials supporting the efficacy and safety of multiple agents for routine prophylaxis used in combination. Therefore, use of concizumab (Alhemo) in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.] is not allowable per policy. There is a lack of head-to-head trials showing superior safety or efficacy comparing concizumab (Alhemo) to other prophylactic agents for the treatment of hemophilia A or B. Given the known safety, established efficacy, and cost-effectiveness of these therapies, prior prophylaxis with emicizumab-kxwh (Hemlibra) remains the preferred specialty agents by this plan due to efficacy, safety, and cost. Concizumab (Alhemo) is specifically more costly than other agents, despite not having any evidence of improved clinical efficacy or safety.

VIII. Concizumab (Alhemo) was studied in the explorer7 trial a Phase 3, open-label, study of 133 adolescent and adult participants with hemophilia A or B with documented history of inhibitor (≥ 0.6 BU). However, only arms 1 and 2 (N=52) were included in the primary efficacy analysis. Previous use of on-demand (OD) therapy with a bypassing agent was required prior to enrollment and participants continued bypassing agents as OD throughout the trial. The mean age was 29 years (range 12 to 79), 80 (60%) with hemophilia A and 53 (40%) with hemophilia B. The primary outcome was a reduction of treated bleeding episodes between concizumab (Alhemo) prophylaxis (arm 2) and no prophylaxis (arm 1).

IX. The results of the explorer7 clinical trial showed that concizumab (Alhemo) prophylaxis demonstrated statistical superiority over treatment with placebo as measured by a reduction in the annualized bleeding rate (ABR). The estimated mean ABR was 1.7 for patients receiving concizumab (Alhemo) prophylaxis and 11.8 for patients not on prophylaxis. Patient reported outcomes did not significantly differ between arms 1 and 2 with respect to bodily pain and physical functioning scores on the 36-Item Short-Form Health Survey (SF-36v2). Patients receiving concizumab (Alhemo) prophylaxis reported improved HRQoL after 24 weeks compared with those receiving no prophylaxis as determined by an estimated treatment difference of −22.6 (95% CI, −42.5; −2.7) points in the Haem-A-QoL total score.

X. While the explorer7 clinical trial was able to show a reduction in bleeding events as compared to placebo there are remaining limitations and unknowns. Specifically, the small sample size of the randomized treatment arms, open-label trial design, insufficient long-term safety data, and lack of comparative efficacy data to other prophylactic hemophilia products. Balancing these concerns there is a need for additional therapies for those with HAwI and HBwI. Inhibitors significantly increase the cost of care and have a negative effect on morbidity and mortality as bleeding episodes become more difficult to treat as compared to those without inhibitors. Therefore, the addition of a once daily, subcutaneous, non-factor therapy could be beneficial to those requiring high doses of factor as well as lessening IV injection burden. Thus, the quality of evidence is considered moderate.

XI. Concizumab (Alhemo) was not directly compared with prophylaxis with emicizumab-kxwh (Hemlibra) therapy for the treatment of hemophilia A. Balancing long-term safety data, efficacy, and costs of alternative therapies compared to concizumab (Alhemo), treatment with emicizumab-kxwh (Hemlibra), when applicable, is required.

XII. 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. Use of on demand

therapy in those with mild-to-moderate disease with less than two instances of spontaneous bleeding is considered clinically appropriate for the management of hemophilia.

XIII. Per the prescribing information maintenance of concizumab (Alhemo) plasma concentration above 200 ng/mL is important to decrease the risk of bleeding episodes. If concizumab (Alhemo) plasma concentration remains below 200 ng/mL at two consecutive measurements, the benefits of continued Alhemo treatment should be evaluated versus the potential risk of bleeding events, and alternative therapies if available should be considered.

XIV. The recommended dosing regimen for concizumab (Alhemo) is as follows:

- Day 1: Loading dose of 1 mg/kg
- Day 2: Once-daily dose of 0.2 mg/kg until individualization of maintenance dose (see below)
    i. Four weeks after initiation of treatment: For dose optimization measure concizumab-mtci plasma concentration by Concizumab Enzyme-Linked Immunosorbent Assay (ELISA) prior to administration of next scheduled dose. An FDA-authorized test for the measurement of concizumab-mtci concentration in plasma is not currently available.
- Once the concizumab-mtci concentration result is available, individualize the maintenance dose of Alhemo. No later than 8 weeks after initiation of treatment, based on the following concizumab-mtci- plasma concentrations:
    i. Less than 200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
    ii. 200 to 4,000 ng/mL: continue once-daily dose of 0.2 mg/kg
    iii. Greater than 4,000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg
- The calculated dose is rounded off to the nearest injectable dose as follows:
    i. 60 mg/1.5 mL (40 mg/mL) in increments of 0.4 mg (brown label)
    ii. 150 mg/1.5 mL (100 mg/mL) in increments of 1 mg (gold label)
    iii. 300 mg/3 mL (100 mg/mL) in increments of 1 mg (white label)

Investigational or Not Medically Necessary Uses

I. Concizumab (Alhemo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Concizumab (Alhemo) used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
        i. Use of dual therapies for routine prophylaxis have not been evaluated for safety and efficacy.
    B. Pediatric patients <12 years of age with hemophilia A or B
        i. Clinical trial data is currently limited to adult and adolescent patients 12 years of age and older.
    C. Hemophilia A & B without inhibitors
        i. The published efficacy data from the explorer7 trial only consisted patients with documented inhibitors. Clinical trials (explorer8) are still ongoing to determine the safety and efficacy of concizumab (Alhemo) in those without inhibitors. A decision on an indication in patients without inhibitors is anticipated July 2025.
    D. Von Willebrand disease

Appendix

The recommended dosing regimen for concizumab (Alhemo) is as follows:

- Day 1: Loading dose of 1 mg/kg
- Day 2 onward: Once-daily dose of 0.2 mg/kg until individualization of maintenance dose (see below)
    - Four weeks after initiation of treatment: For dose optimization measure concizumab-mtci plasma concentration by Concizumab Enzyme-Linked Immunosorbent Assay (ELISA) prior to administration of next scheduled dose. An FDA-authorized test for the measurement of concizumab-mtci concentration in plasma is not currently available.
- Once the concizumab-mtci concentration result is available, individualize the maintenance dose of Alhemo. No later than 8 weeks after initiation of treatment, based on the following concizumab-mtci- plasma concentrations:
    - Less than 200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
    - 200 to 4,000 ng/mL: continue once-daily dose of 0.2 mg/kg
    - Greater than 4,000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg
- The calculated dose is rounded off to the nearest injectable dose as follows:
    - 60 mg/1.5 mL (40 mg/mL) in increments of 0.4 mg (brown label)
    - 150 mg/1.5 mL (100 mg/mL) in increments of 1 mg (gold label)
    - 300 mg/3 mL (100 mg/mL) in increments of 1 mg (white label)

References

1. Alhemo. Package Insert. Novo Nordisk, Inc; December 2024.
2. Overview of the explorer Clinical Development Program for Concizumab. Novo Nordisk. January 13, 2025.
3. Matsushita T, Shapiro A, Abraham A, Angchaisuksiri P, Castaman G, Cepo K, d'Oiron R, Frei-Jones M, Goh AS, Haaning J, Hald Jacobsen S, Mahlangu J, Mathias M, Nogami K, Skovgaard Rasmussen J, Stasyshyn O, Tran H, Vilchevska K, Villarreal Martinez L, Windyga J, You CW, Zozulya N, Zulfikar B, Jiménez-Yuste V; explorer7 Investigators. Phase 3 Trial of Concizumab in Hemophilia with Inhibitors. N Engl J Med. 2023 Aug 31;389(9):783-794.
4. Tran H, von Mackensen S, Abraham A, Castaman G, Hampton K, Knoebl P, Linari S, Odgaard-Jensen J, Neergaard JS, Stasyshyn O, Thaung Zaw JJ, Zulfikar B, Shapiro A. Concizumab prophylaxis in persons with hemophilia A or B with inhibitors: patient-reported outcome results from the phase 3 explorer7 study. Res Pract Thromb Haemost. 2024 Jun 17;8(4):102476.
5. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Hemophilia. 2020: 26(Suppl 6): 1-158.
6. Meeks SL, Batsuli G. Hemophilia and inhibitors: current treatment options and potential new therapeutic approaches. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):657-662.
7. Novo Nordisk. FDA approves Alhemo® injection as once-daily prophylactic treatment to prevent or reduce the frequency of bleeding episodes for adults and children 12 years of age and older with hemophilia A or B with inhibitors. Novodordisk.com. December 20, 2024. Accessed January 23, 2025. News detailshttps://www.novonordisk-us.com/media/news-archive/news-details.html?id=915084

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
emicizumab-kxwh (Hemlibra®) – Hemophilia A	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors
Standard Half-life Factor VIII Products – Hemophilia A	On-demand Treatment
	Routine Prophylaxis

	Perioperative Management
Standard Half-life Factor IX Products – Hemophilia B	Control and prevention of bleeding episodes
	Perioperative management
	Routine Prophylaxis
Bypassing Agents – Hemophilia A & B	Control and prevention of bleeding – Hemophilia A or B with inhibitors
	Routine prophylaxis – Hemophilia A or B with inhibitors
	Perioperative management – Hemophilia A or B with inhibitors
	Control and prevention of bleeding episodes – Acquired hemophilia
	Control and prevention of bleeding episodes – Factor VII deficiency
	Control and prevention of bleeding episodes – Glanzmann's Thrombasthenia
	Perioperative management – acquired hemophilia
	Perioperative management – factor VII deficiency
	Perioperative management – Glanzmann's Thrombasthenia
Extended Half-life Factor VIII Products – Hemophilia A	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management
Extended Half-life Factor IX Products – Hemophilia B	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management
marstacimab (Hympavzi™)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with Hemophilia A or Hemophilia B without factor inhibitors
Fitusiran (Qfitlia)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent (≥12 years old) patients with hemophilia A or B with or without inhibitors

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2025

Policy Type: PA/SP Pharmacy Coverage Policy: UMP107

Description

Continuous Glucose Monitors (CGMs) are blood glucose monitoring systems used to manage patients with diabetes mellitus that are insulin dependent.

Length of Authorization

- **Dexcom and Freestyle Libre CGM products**
  - Initial: Length of benefit
  - Renewal: Length of benefit

- **All other CGM products (e.g. Medtronic, Eversense, etc.)**
  - Initial: 12 months
  - Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
Dexcom G6	Diabetes Mellitus	System meter	1 meter per 365 days
		Transmitter	1 transmitter per 90 days
		Sensors	3 sensors (1 kit) per 30 days
Dexcom G7		System meter	1 meter per 365 days
		Sensors	3 sensors (1 kit) per 30 days
Freestyle Libre		Reader	1 reader per 365 days
		Sensor (14 day)	2 sensors per 28 days
Freestyle Libre 3-Plus Sensor		Sensor (15 day)	2 sensors per 30 days
Medtronic Guardian CGM		Transmitter	1 transmitter per 365 days
		Sensor	5 sensors per 30 days
Medtronic Simplera and Simplera Sync CGM		Sensor	4 sensors per 28 days
Eversense CGM system		Transmitter	1 transmitter per 365 days
		Sensor	1 sensor per 90 days

Dexcom G6, Dexcom G7, and Freestyle Libre are the preferred CGM products.

- There is no prior authorization required on these preferred products, unless requesting over the allowed quantity limits noted above. **Step therapy may apply.**

Initial Evaluation

I. **All other CGM products (e.g. Medtronic, Eversense, etc.)** may be considered medically necessary when the following criteria below are met:

A. Member has a diagnosis of one of the following:

1. **Type I Diabetes**; **AND**
    i. Member is currently on insulin therapy; **OR**
2. **Type II Diabetes; AND**
    i. Member is currently on insulin therapy; **AND**
        a. Unable to achieve HbA1c goal despite adherence to an appropriate glycemic management plan (e.g intensive insulin therapy; testing glucose more than 4 times per day); **OR**
        b. Experiencing one or more severe (blood glucose < 50 mg/dl or symptomatic) episodes of hypoglycemia despite adherence to an appropriate glycemic management plan (e.g. frequent adjustments in medication regimen; testing blood glucose 4 or more times per day); **OR**
        c. Unable to recognize, or communicate, symptoms of hypoglycemia; **OR**
3. **Diabetes in pregnancy**; **AND**
    i. Type 1 diabetes; **OR**
    ii. Type 2 diabetes; **OR**
    iii. Gestational diabetes; **AND**

B. Use of **Dexcom** AND **Freestyle Libre** products have been ineffective, not tolerated, or not indicated; **OR**
    1. Member uses an insulin pump not compatible with preferred Dexcom or Freestyle Libre CGM products (e.g Medtronic MiniMed)

Renewal Evaluation

I. If the initial diagnosis was gestational diabetes, a diagnosis of ongoing diabetes (e.g., type 2 diabetes) has been established; **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 [i.e., HbA1c within target, improved hypoglycemic awareness, or decreased hypoglycemic episodes].

Supporting Evidence

I. In a study conducted by the Effective Health Care Program of the US Agency for Healthcare Research and Quality, where they conducted comparative effectiveness research assessing glucose monitoring (GM) methods and intensive insulin therapy methods, noted a lower A1c by 0.3% in patients who used CGM compared to conventional blood glucose monitoring (BGM). Although this method of glucose monitoring did not affect patient quality of life overall, the positive outcome of a lowered A1c was consistent in patients <18 years of age, thereby supporting the recommendation for CGM in adolescent patients and children.
II. The 2016, the American Association of Clinical Endocrinologists and American College of Endocrinology glucose monitoring consensus recommends the use of a CGM in adults with Type 1 diabetes. In adults with type 2 diabetes, the consensus recommends a structured blood

glucose management (BGM) in patients receiving insulin, sulfonylureas, or glinides (prandial glucose regulators) , the consensus does not have a recommendation for the use of CGM in these patients but note that data for a CGM in patients with type 2 diabetes is limited.

III. The American Diabetes Associated International Consensus on Use of Continuous Glucose Monitoring recommended a CGM system to patients with type 1 diabetes and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia.

IV. In a randomized controlled trial (CONCEPTT) of CGM systems in addition to standard care on pregnant women with type 1 diabetes, the value of CGM in pregnancy was demonstrated by showing a mild improvement in A1c without an increase in hypoglycemia and reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia.

V. According to Dexcom, the G6 system is compatible with the t:slim X2™ Insulin Pump and Omnipod®.
Minimed™ offers 2 insulin pump systems that are compatible with select CGMs. The Minimed™ 770G System which can be used with Medtronic products (e.g. reservoir, infusion sets, Guardian™ Link 3 Transmitter, Guardian™ Sensor 3) and Accu-Chek® Guide Link Blood Glucose Meter. On the other hand, the Minimed™ 630G insulin pump is only compatible with the Contour® NEXT LINK 2.4 meter.

VI. The UMP Policy for Continuous Glucose Monitoring systems aligns with the Washington Health Care Authority (HCA) Health Technology Clinical Committee (HTCC) policy. The determinations of the HTCC are required to be followed by state purchased health care programs including Uniform Medical Plan. Glucose monitoring | Washington State Health Care Authority

References

1. Bailey TS, Grunberger G, Bode BW, et al. American Association of Clinical Endocrinologists and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement. Endocr Pract. 2016;22(No. 2) 231-261.
2. Peters AL, Ahmann AJ, Battelino T, et al. Diabetes Technology—Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, November 2016, 101(11):3922–3937.
3. Danna T, Nimri R, Battelino T, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 2017 Dec; 40(12): 1631-1640.
4. Dexcom G6 Integrations and Compatability. Dexcom website. Accessed December 4, 2020. https://www.dexcom.com/g6/integrations-and-compatibility#:~:text=The%20only%20available%20pump%20with,help%20manage%20type%201%20diabetes.
5. MiniMed 630G System Support. Medtronic website. Accessed December 7, 2020. https://www.medtronicdiabetes.com/customer-support/minimed-630g-system-support/linking-your-pump-to-a-meter.
6. Minimed 770G System. Medtronic website. Accessed December 7, 2020. https://www.medtronicdiabetes.com/products/minimed-770g-insulin-pump-system.
7. Eversense CGM system website. Accessed June 11, 2021. https://www.eversensediabetes.com/
8. Dexcom G7 system. Dexcom website. https://www.dexcom.com/en-us/g7-cgm-system

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to align with HTCC updates from May 2025: removed policy criteria for Dexcom and Freestyle CGM. For non-preferred products: removed age requirement, added step through insulin for a diagnosis of T1DM and T2DM, and removed insulin requirement for diabetes in pregnancy	08/2025
Updated length of authorization to length of benefit for Dexcom and Freestyle Libre CGM	01/2025

Added freestyle libre 3 plus sensor	06/2024
Update to Medtronic sensor QL from 5 sensors in 35 days to 5/30	10/2023
Added requirement that member must test 4x/day and have intensive insulin therapy to qualify for CGM use	07/2023
Added Medtronic Gaurdian 4 to the policy	06/2023
Effective 04/01/2023: Added Dexcom G7 CGM system to policy	03/2023
Updated language to better capture intent; updated non-preferred criteria to be more encompassing to all non-formulary products	08/2022
Added Eversense CGM system to policy under non-preferred status	07/2021
Policy created	12/2020

crinecerfont (Crenessity™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP322

Description

Crinecerfont (Crenessity) is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist orally administered twice daily.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
crinecerfont (Crenessity)	Adjunct to glucocorticoid replacement to control androgens in adults and pediatrics with classic congenital adrenal hyperplasia (CAH)	25 mg capsules 50 mg capsules 100 mg capsules	60 capsules/30 days
		50 mg/mL solution	120 mL/30days

Initial Evaluation

I. **Crinecerfont (Crenessity)** 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, an endocrinologist; **AND**
   C. A diagnosis of classic 21-hydroxylase deficiency **congenital adrenal hyperplasia (CAH)** confirmed by one of the following:
      1. Positive newborn screening; **OR**
      2. Positive laboratory testing (e.g., Elevated 17-hydroxyprogesterone (17-OHP) level, positive CYP21A2 genotype, cosyntropin stimulation test, etc.); **AND**
   D. Member is currently taking long-term (> 6 months), supraphysiological glucocorticoid treatment for congenital adrenal hyperplasia (e.g., hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone); **AND**
   E. Provider attestation that medication will be used as adjunctive treatment with glucocorticoid replacement therapy; **AND**
   F. Provider attestation that the medication will not be used in combination with a strong CYP3A4 or CYP2B6 inducer(s) (e.g., carbamazepine, phenobarbital, valproic acid, phenytoin, rifampin, ritonavir); **OR**
      1. Provider attestation that the appropriate dose adjustment will be made while using a strong CYP3A4 or CYP2B6 inducer(s)

II. Crinecerfont (Crenessity) is considered investigational when used for all other conditions, including but not limited to:

A. Crinecerfont (Crenessity) is used in conditions other than classic CAH that require long-term glucocorticoid therapy.
B. Non-classic CAH
C. Crinecerfont (Crenessity) used in classic CAH not due to 21-hydroxylase 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. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in glucocorticoid dose, reduction in 17-hydroxyprogesterone (17-OHP) level, reduction in androstenedione level]; **AND**
IV. Provider attestation that the member will continue to use crinecerfont (Crenessity) in combination with glucocorticoid replacement therapy; **AND**
V. Provider attestation that the medication will not be used in combination with a strong CYP3A4 or CYP2B6 inducer(s) (e.g., carbamazepine, phenobarbital, valproic acid, phenytoin, rifampin, ritonavir); **OR**
    - Provider attestation that the appropriate dose adjustment will be made while using a strong CYP3A4 or CYP2B6 inducer(s)

Supporting Evidence

I. Crinecerfont (Crenessity) is a selective corticotropin-releasing factor (CRF) type 1 receptor antagonist, FDA-approved as adjunct therapy with glucocorticoid replacement in patients with classic congenital adrenal hyperplasia (CAH) due to a 21-hydroxylase deficiency. The CAHtalyst trial did not enroll any participants under 4 years old; therefore, there is no efficacy and safety data supporting the use of crinecerfont (Crenessity) in this population.
II. In the United States, all newborns are screened for 21-hydroxylase deficiency CAH between two to four days after birth. According to 2018 guidelines from the Endocrine Society (ES), a referral to a pediatric endocrinologist is recommended if an infant has a positive newborn screening for CAH.
III. Evaluation of cosyntropin stimulation testing can be done to confirm the diagnosis after positive newborn screening. In symptomatic patients beyond infancy, screening of early-morning baseline serum 17-OHP levels is recommended, and typically done using liquid chromatography-tandem mass spectrometry. For patients with borderline 17-OHP levels, a complete adrenocortical profile is recommended after a cosyntropin stimulation test to differentiate 21-hydroxylase deficiency from other enzyme defects. Genotyping is also a diagnostic tool for patients with CAH if cosyntropin stimulation tests are ambiguous or cannot be accurately performed.
IV. The 2018 Endocrine Society guidelines recommend hydrocortisone as the preferred first-line maintenance therapy for growing individuals with classic CAH. However, the guidelines recommend against the use of oral hydrocortisone suspension and chronic use of long-acting

potent glucocorticoids in this population due to the increased risk of growth suppression in children. In adults with classic CAH, daily hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids are recommended. Clinical practice guidelines from the American Academy of Family Physicians (AAFP) also provide similar recommendations for first-line treatment.

V. Crinecerfont (Crenessity) was studied in two Phase 3, multicenter, randomized, double-blind, placebo-controlled trials.
    - One trial included adults 18 years and older (CAHtalyst Adult); and the other included individual aged 2 to 17 years (CAHtalyst Pediatric). The CAHtalyst Adult trial included 182 participants, with an average age of 30 years, who received supraphysiological daily glucocorticoid dose >13 mg/m^2 of HC-equivalent. Participants were randomized 2:1 to receive crinecerfont (Crenessity) or placebo for 24 weeks. During treatment, baseline glucocorticoid regimen was strategically reduced to achieve the lowest glucocorticoid dose possible while still maintaining androstenedione control. The primary endpoint for the CAHtalyst Adult trial was the percentage change in the daily glucocorticoid dose from baseline to week 24 while maintaining androstenedione control. By the end of week 24, the crinecerfont (Crenessity) arm achieved a statistically significant percentage change in glucocorticoid dose compared to placebo (-27.3 vs -10.3; P<0.001).
    - The CAHtalyst Pediatric trial included 103 participants, averaging 12 years of age, who received daily glucocorticoid dose >12 mg/m^2 of HC-equivalent. Similarly to CAHtalyst Adult trial, the glucocorticoid regimen was reduced but had a target dose of 8-10 mg/m^2 of HC-equivalent while maintaining androstenedione control by week 28. The primary endpoint in the pediatric trial was the change in androstenedione levels from baseline to week 4. By week 4, CAHtalyst Pediatric trial also achieved a statistically significant primary endpoint (-197 vs 71; P<0.001).

VI. Crinecerfont (Crenessity) is the first adjunctive agent approved for the management of classic CAH. The current mainstay approach for managing classic CAH is glucocorticoid and/or mineralocorticoid replacement therapy.

VII. The CAHtalyst trials specifically excluded concomitant therapy use of strong inducers of CYP3A4 or CYP2B6. There is no safety data from clinical trials that demonstrates appropriate concomitant use of crinecerfont (Crenessity) with certain CYP inducers. However, the FDA label includes instructions for dose adjustment with concomitant use of CYP inducers with crinecerfont (Crenessity). A dose increase of up to two times the standard recommended dose is advised when crinecerfont (Crenessity) is used in combination with a strong CYP3A4 inducer, and a dose increase of 1.5 times the standard recommended dose is advised when used in combination with a moderate CYP3A4 inducer (see appendix for examples).

Investigational or Not Medically Necessary Uses

I. Crinecerfont (Crenessity) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Crinecerfont (Crenessity) is used in any conditions other than classic CAH that require long-term glucocorticoid therapy.
      i. There are no current data or investigations on the use of crinecerfont (Crenessity) in any conditions other than CAH that requires chronic glucocorticoid replacement therapy. CAHtalyst trials excluded any conditions outside CAH that require glucocorticoid dosing; thus, there is no efficacy and safety evidence to suggest clinical benefit of crinecerfont (Crenessity) in any other conditions.
   B. Non-classic CAH
      i. Non-classic CAH is considered the mild form of the condition. Patients with non-classic CAH often exhibit mild to no symptoms or clinical presentation. The risks of treatment may outweigh the benefits in this population; thus, this indication is considered experimental and investigational at this time.
   C. Crinecerfont (Crenessity) used in classic CAH not due to 21-hydroxylase deficiency
      i. Crinecerfont (Crenessity) was only studied in patients who have 21-hydroxylase deficiency classic CAH.
      ii. There is a lack of evidence to support the use to crinecerfont (Crenessity) in CAH due to other enzyme deficiency.

Appendix

I. Table 1: CYP3A4 and CYP2B6 inducers

	CYP3A4 inducers	**CYP2B6 inducers**
Strong inducers	Carbamazepine Dexamethasone Fosphenytoin Lumacaftor Midostaurin Mitotane Phenobarbital Phenytoin Primidone Rifampin St. John's Wort	Carbamazepine Fosphenytoin Nevirapine Phenobarbital Phenytoin
Moderate inducers	Bosentan Dexamethasone Efavirenz Etravirine Modafinil Nafcillin	Alpelisib Rifampin

** This table includes only common examples and is not a comprehensive list.*

References

1. Crenessity product dossier. Neurocrine Biosciences, Inc; August 2024.
2. Crenessity. Package Insert. Neurocrine Biosciences, Inc; December 2024.
3. Endocrine Society. Congenital Adrenal Hyperplasia Guideline Resources. September 19, 2018. Accessed February 19, 2025. Congenital Adrenal Hyperplasia Guideline Resources | Endocrine Society
4. Deaton, M.A, Glorioso, J.E., & Mclean, D.B. Congenital Adrenal Hyperplasia: Not Really a Zebra. *American Family Physician*. 1999;59(5):1190-1196. https://www.aafp.org/pubs/afp/issues/1999/0301/p1190.html.

5. Auchus RJ, Hamidi O, Pivonello R, et al. Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia. N Eng J Med. 2024;391:504-514. DOI: 10.1056/NEJMoa2404656.
6. Sarafoglou K, Kim MS, Lodish M, et al. Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia. N Eng J Med. 2024;391:493-503. DOI: 10.1056/NEJMoa2404655.
7. Sharma L, Momodu II, & Singh G. Congenital Adrenal Hyperplasia. National Library of Medicine. Update January 27, 2025. Accessed February 20, 2025. Congenital Adrenal Hyperplasia - StatPearls - NCBI Bookshelf

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2025

Cushing's Syndrome/Disease

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP268

Description

Pasireotide diaspartate (Signifor) is a subcutaneous somatostatin analog solution that exerts its activity by binding to somatostatin receptors causing adrenocorticotropic hormone (ACTH) secretion to be inhibited thereby leading to decreased cortisol secretion.

Osilodrostat (Isturisa) is an orally administered cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

Levoketoconazole (Recorlev), the 2S,4R enantiomer of ketoconazole, is an orally administered steroidogenesis inhibitor that reduces endogenous cortisol levels.

Mifepristone (Korlym) is a cortisol receptor blocker indicated for hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pasireotide diaspartate (Signifor®)	Cushing's Disease	0.3 mg/mL ampule	60 ampules/30 days
		0.6 mg/mL ampule	
		0.9 mg/mL ampule	
osilodrostat (Isturisa®)		1 mg tablets	360 tablets/30 days
		5 mg tablets	
levoketoconazole (Recorlev®)	Cushing's Syndrome	150 mg tablets	240 tablets/30 days
mifepristone (Korlym®)	Hyperglycemia secondary to hypercortisolism in Cushing's syndrome	300 mg tablets	120 tablets/30 days (not to exceed 20 mg/kg/day)
Provider Administered Agents*			
pasireotide pamoate (Signifor LAR®)	Acromegaly, Cushing's disease	10 mg vial	1 vial/28 days
		20 mg vial	
		30 mg vial	
		40 mg vial	
		60 mg vial	

**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*

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Initial Evaluation

I. **Pasireotide diaspartate (Signifor) and osilodrostat (Isturisa)** 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 endocrinologist; **AND**
   C. Will not be used in combination with other agents listed in this policy (e.g., pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and/or mifepristone (Korlym)); **AND**
   D. A diagnosis of **Cushing's disease** when the following are met:
      1. Member had inadequate response to pituitary surgical resection; **OR**
         i. Member is not a candidate for pituitary surgery; **AND**
      2. Treatment with TWO of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Ketoconazole; **OR**
         ii. Cabergoline (Dostinex); **OR**
         iii. Metyrapone (Metopirone)*; **OR**
         iv. Mitotane (Lysodren); **AND**
      3. The request is for pasireotide diaspartate (Signifor); **OR**
      4. The request is for osilodrostat (Isturisa); **AND**
         i. Treatment with pasireotide diaspartate (Signifor) has been ineffective, contraindicated, or not tolerated

II. **Levoketoconazole (Recorlev)** 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 endocrinologist; **AND**
   C. Levoketoconazole (Recorlev) will not be used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym); **AND**
   D. A diagnosis of **Cushing's syndrome** when the following are met:
      1. Member had inadequate response to pituitary surgical resection; **OR**
         i. Member is not a candidate for pituitary surgery; **AND**
      2. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
         i. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
      3. Treatment with ALL of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Cabergoline (Dostinex); **AND**
         ii. Metyrapone (Metopirone)*; **AND**
         iii. Mitotane (Lysodren); **AND**
         iv. Pasireotide diaspartate (Signifor)*

III. **Mifepristone (Korlym)** 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 endocrinologist; **AND**
   C. Mifepristone (Korlym) will not be used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or levoketoconazole (Recorlev); **AND**
   D. A diagnosis of **hyperglycemia secondary to hypercortisolism in members with endogenous Cushing's syndrome** when the following are met:
      1. Member had inadequate response to pituitary surgical resection; **OR**
         i. Member is not a candidate for pituitary surgery; **AND**
      2. Member has a diagnosis of type 2 diabetes OR glucose intolerance; **AND**
         i. Baseline hemoglobin A1c (HbA1c) has been provided in this request; **AND**
      3. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of generic oral mifepristone tablets; **OR**
         i. Documentation of serious adverse effect or allergy with generic oral mifepristone; **AND**
      4. Treatment with ALL of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Ketoconazole; **AND**
         ii. Cabergoline (Dostinex); **AND**
         iii. Metyrapone (Metopirone)*; **AND**
         iv. Mitotane (Lysodren); **AND**
         v. Pasireotide diaspartate (Signifor)*

IV. Pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), mifepristone (Korlym) are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Hypertension associated with Cushing's syndrome
   B. Termination of pregnancy
   C. Induction of labor
   D. Treatment of fungal infections

V. Pasireotide diaspartate (Signifor), Osilodrostat (Isturisa), levoketoconazole (Recorlev), mifepristone (Korlym) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Use in combination with other agents used for Cushing's syndrome
   B. Exogenous (Iatrogenic) Cushing's syndrome
   C. Acromegaly
   D. Pancreatic fistula, postoperative/prophylaxis
   E. Carcinoid syndrome
   F. Neuroendocrine tumor

G. VIPoma
H. Hyperglycemia secondary to Type 2 diabetes (not associated with endogenous Cushing's 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. Medication requested will not be used in combination with other agents listed in this policy (e.g., pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and/or mifepristone (Korlym)); **AND**
IV. The request is for one of the following:
    A. **Pasireotide diaspartate (Signifor)**; **AND**
        1. Member has exhibited improvement or stability of disease symptoms (e.g. cortisol level has decreased from baseline); **OR**
    B. **Osilodrostat (Isturisa); AND**
        1. Member has exhibited improvement or stability of disease symptoms (e.g. cortisol level has decreased from baseline); **OR**
    C. **Levoketoconazole (Recorlev); AND**
        1. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
            i. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
        2. Member has exhibited improvement or stability of cortisol levels and disease symptoms (e.g., improvement in cushingoid appearance, acne, hirsutism, psychiatric symptoms, body weight); **OR**
    D. **Mifepristone (Korlym); AND**
        1. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of generic oral mifepristone tablets; **OR**
            i. Documentation of serious adverse effect or allergy with generic oral mifepristone; **AND**
        2. Member experienced a reduction in HbA1c from baseline; **AND**
        3. Member has exhibited improvement in Cushing's syndrome symptoms (e.g., cushingoid appearance, acne, hirsutism, psychiatric symptoms, and excess total body weight).

Supporting Evidence

I. Cushing's disease is a disorder that leads to excess cortisol (hypercortisolemia) and is usually due to a corticotropin (ACTH)-producing pituitary (Cushing's disease). In Cushing's syndrome, ACTH levels are not always elevated, and symptoms of high cortisol can be caused by

corticosteroid or an adrenal tumor. Diagnosis and management of Cushing's syndrome is complex and requires confirmatory tests (e.g., urinary free cortisol (UFC), salivary cortisol) as well as close monitoring by, or in consultation with, an endocrinologist.

II. Cushing's disease and Cushing's syndrome are caused by pathological hypercortisolism that includes demonstrable clinical features. Hallmark symptoms of high levels of cortisol include clinical features such as weight gain, hypertension, high blood glucose, and depression. The goals of treatment are to eliminate its primary cause and achieve remission so as to eliminate the associated signs, symptoms, and comorbidities and to improve quality of life (QOL).

III. According to the Endocrine Society Clinical Practice Guidelines and Pituitary Society Consensus Guidelines for Cushing's disease, first line treatment for excess cortisol production due to Cushing's syndrome is transsphenoidal surgery (TSS) regardless of the cause. Although surgical treatment is optimal with a success rate of 80-85%, second-line medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Repeat TSS is indicated in patients with recurrent Cushing's syndrome symptoms and have evidence of residual visible tumor on MRI. There is low quality evidence recommending systemic therapy to treat Cushing's syndrome in the pre-operative setting. Pre-operative therapy with systemic treatment or targeted radiation may be considered for patients with aggressive Cushing's syndrome, defined as those with life-threatening severe clinical features to rapidly reduce or stabilize cortisol levels.

IV. Systemic therapy options for Cushing's consist of steroidogenesis inhibitors (i.e., ketoconazole, metyrapone, mitotane, osilodrostat, etomidate), pituitary-directed agents (i.e., cabergoline, pasireotide), and glucocorticoid antagonists (i.e., mifepristone). Only levoketoconazole (Recorlev), osilodrostat (Isturisa), and pasireotide (Signifor) are FDA-approved to treat Cushing's in patients which pituitary surgery is not an option or has not been curative. Ketoconazole, metyrapone, mitotane, etomidate, and cabergoline are used off-label.

V. Guidelines recommend steroidogenesis inhibitors (i.e., ketoconazole, osilodrostat, metyrapone, etomidate) as first-line pharmacologic therapy following non-curative surgery or in patients for whom surgery was not an option. Among these therapies, ketoconazole is strongly recommended due to ease of dose titration and availability. Efficacy of ketoconazole in Cushing's syndrome is based on several retrospective trials that report UFC normalization in 45-50% of patients. IV anesthetic, etomidate, has a rapid onset of action, but use is limited to acute treatment of severe hypercortisolism due to Cushing's syndrome. Second-line systemic therapies may include any of the remaining agents (i.e., pituitary-directed agents, glucocorticoid antagonists, etc.) as treatment selection is individualized based on severity of disease, clinical manifestations, cost, drug accessibility, and safety profile. As of February 2023, guidelines have not been updated with regard to place in therapy for osilodrostat (Isturisa) or levoketoconazole (Recorlev) for the treatment of Cushing's syndrome.

VI. Guidelines do not specify a preferred treatment algorithm, nor do they indicate that treatment failure to one agent precludes treatment with another agent in the same class. The Pituitary Society guidelines recommend switching therapies when cortisol levels remain elevated despite treatment on maximum tolerated dose for 2-3 months.

VII. There is a lack of head-to-head trials showing superior safety or efficacy comparing levoketoconazole to ketoconazole, cabergoline (Dostinex), metyrapone (Metopirone), mitotane (Lysodren), or pasireotide diaspartate (Signifor). Given the known safety, established efficacy,

and cost-effectiveness of these therapies, pasireotide diaspartate (Signifor) remains the preferred specialty agent by this plan due to efficacy, safety, and cost. Osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) are significantly more costly than pasireotide diaspartate (Signifor), despite not having any evidence of improved clinical efficacy or safety.

VIII. The safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) has been studied in patients 18 years of age or older, and there is no published data to support its use in pediatric patients.

IX. The efficacy of pasireotide was demonstrated in a 12-month, randomized, Phase III study. The study looked at 162 patients with Cushing's disease with persistent or recurrent disease despite pituitary surgery or new patients whom surgery was not indicated or who had had refused surgery. Cushing's disease was defined by a mean 24-hour urinary free cortisol (UFC) level of at least 1.5 times the upper limit of the normal range (ULN). Patients enrolled were randomized to receive pasireotide at 0.6 mg twice daily (n = 82) or 0.9 mg twice daily (n = 80). Three months after randomization patients were reassessed for efficacy, which was defined as having a 24-hour UFC ≤2.0 ULN or equal to their baseline values. If they were considered responders they were continued at their randomized dose until month six. If the patient did not fall into those responder parameters the patient and provider were unblinded and their dose was increased by 0.3 mg bid. At month six all the patients were transferred into the open label portion of the study, where their dose of pasireotide could be increased (to a max of 1200 mg bid) to achieve UFC under the upper limit of the normal range. At this time doses could also be decreased if needed for adverse events.

- The primary outcome was the proportion of patients who achieved normalization of mean 24-hour UFC levels (UFC ≤ULN) after 6 months of treatment without a dose increase of pasireotide. Secondary outcomes included signs and symptoms of Cushing's disease including morning cortisol levels, blood pressure, LDL and weight changes (please review study for others).
- Results showed after 6 months, 15% (12 patients) and 26% (21 patients) of patients in the 0.6 mg and 0.9 mg groups respectively reached the primary endpoint (normalization of mean 24-hour urinary free cortisol UFC levels). Secondary outcomes also showed statistically significant changes including: diastolic blood pressure: −3.7 mm Hg P=0.03, LDL cholesterol: −15 mg/deciliter P<0.001 and weight: −6.7 kg P<0.001.
- The open label portion of the study showed continuing benefits with 13% of patients in the 0.6 mg group and 25% of those in the 0.9 mg group had urinary free cortisol levels at or below the upper limit of the normal range at month 12.

X. The safety and efficacy of osilodrostat (Isturisa) was assessed in one 48-week, prospective, multicenter, open-label, phase III trial with a double-blind, placebo-controlled, randomized withdrawal period in 137 patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. The trial included patients who were previously treated (87.6% had previous pituitary surgery and 74.5% had previous medical therapy for Cushing's disease, including ketoconazole, metyrapone, cabergoline, and pasireotide (Signifor/Signifor LAR).

- The primary efficacy outcome was the proportion of patients maintaining complete response a mean urinary free cortisol (mUFC) ≤ upper limit of normal (ULN) without

a dose increase during the randomized withdrawal period at week 34. At the time of the randomization (Week 26) all (100%) randomized patients were biochemically controlled (mUFC ≤ ULN).

- At the end of the 8-week randomized withdrawal period (Week 34 of study), the complete response rate in the osilodrostat (Isturisa) group dropped to 86.1% but was higher than that in the placebo group (29.4%).
- About 53% of patients met the key secondary endpoint, the proportion of patients with mUFC≤ULN at week 24 (end of open-label osilodrostat treatment period 2) without dose-up titration weeks 13-24.
- Most common adverse reactions (incidence >20%) were adrenal insufficiency, fatigue, nausea, headache, and edema.
- Although osilodrostat (Isturisa) showed a statistically significant improvement in the control of the cortisol levels, clinical significance, durability of response, meaningfulness of these results are unknown and the quality of evidence is low.

XI. Ketoconazole is a racemic mixture of two enantiomers, one of which is levoketoconazole. Levoketoconazole (Recorlev) is the pure (2S, 4R) enantiomer and is FDA approved for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.

XII. Levoketoconazole (Recorlev) has not been evaluated against ketoconazole for the treatment of hypercortisolemia in patients with Cushing's syndrome, therefore comparative safety and efficacy remain uncertain. However, the chemical entity in ketoconazole is the same as levoketoconazole (Recorlev); therefore, both products are expected to produce a similar efficacy and safety profile for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome, even in the absence of an FDA-labeled indication for ketoconazole. Furthermore, medical necessity for levoketoconazole (Recorlev) is limited to members that have a documented serious intolerance (e.g., allergy reaction, serious adverse event, life-threatening reaction that required hospitalization) or treatment failure with generic oral ketoconazole. If a member has a contraindication to ketoconazole, it is presumed that treatment with levoketoconazole would also be contraindicated, given similar warnings and side effect profile.

XIII. Levoketoconazole (Recorlev) has been studied in two phase 3 studies for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.

- The SONICS trial was a 6-month open-label, single arm, dose-titration study (n=95) with a 21-week run-in period; patients who did not achieve a stable therapeutic dose during this dose titration phase did not continue in the study. The primary efficacy endpoint was the proportion of patients with normalized mean urinary free cortisol (mUFC) response of at the end of a 6-month maintenance phase without a dose increase. About 30% of patients on levoketoconazole achieved a normalized mUFC (95% CI: 21.7%- 41.2%; p=0.0154) at 6 months. Significant mean improvements in comorbidity biomarkers and clinical signs and symptoms were also seen (glucose metabolism, total cholesterol, LDL, HDL, body weight, and hirsutism (women)). Approximately 15% of patients had at least one treatment-related serious adverse event, which include reversible liver-related adverse events, QT prolongation, and adrenal insufficiency. Routine laboratory assessments showed ALT increases above the ULN in 41% of patients at any time. Notably, 51% of study

participants discontinued therapy with the most common reasons being adverse events and inefficacy.

- The LOGICS trial was 6-month double-blind, randomized, placebo-controlled withdrawal and rescue/restoration study of patients who completed the SONICS trial (n=12) or were treatment-naïve (n=72). A total of 84 patients were enrolled in the study, of whom 44 entered the randomized withdrawal phase and were assigned 1:1 to placebo or levoketoconazole. The primary outcome was the proportion of patients with loss of mUFC response, which was met with a 40% loss of response in the levoketoconazole group compared to 95% of patients in the placebo group (p=0.0002). A secondary endpoint, mUFC normalization, was met with 50% of patients achieving normalized mUFC in the levoketoconazole group compared to 4.5% of patients on placebo (95% CI: 19.2-67.9; P=0.0015). Approximately 48% of patients discontinued the study before the double-blind phase due to treatment related adverse events. Additionally, 95% of patients required rescue therapy due to high mUFC levels during the randomized withdrawal phase.

XIV. Long term safety and efficacy of levoketoconazole has not been established; however, an ongoing trial (OPTIC study) is currently evaluating long-term use of levoketoconazole in patients that have completed the SONICS and LOGICS trials.

XV. The overall quality of evidence for levoketoconazole (Recorlev) is considered low due to open-label study design, lack of an active or meaningful comparator given high volume of concomitant rescue therapy, and high attrition rate. While UFC is a clinically meaningful, objective endpoint correlated with improvement of hypercortisolism in Cushing's syndrome, concerns listed above limit confidence that medication is providing a clinically meaningful benefit over available treatments for Cushing's syndrome. Additionally, levoketoconazole use was associated with serious safety concerns including hepatotoxicity and QT prolongation.

XVI. It is known that patients with Cushing's have various lab abnormalities and may develop type 2 diabetes secondary to elevated cortisol levels. The difference between mifepristone (Korlym) and the other agents for Cushing's is that mifepristone (Korlym) was evaluated for treating hyperglycemia secondary to hypercortisolism in patients with CS who have T2DM. Korlym has not been evaluated to lower cortisol levels, however mifepristone has been used off-label for this; no other drugs approved for CS have such an indication.

XVII. Mifepristone acts as a rapid acting glucocorticoid receptor antagonist. The safety and efficacy of mifepristone (Korlym) for the treatment of endogenous Cushing's syndrome was studied in an uncontrolled, open-label, 24-week, multicenter clinical study that enrolled 50 participants. Those participants exhibited clinical and biochemical evidence of hypercortisolemia despite first-line intervention via surgical treatment and radiotherapy. Per label, the reasons for medical treatment was failed surgery, recurrence of disease, and a poor medical candidate for surgery. The study was split into two cohorts: diabetes and hypertension. The primary efficacy endpoint for the diabetes cohort was a ≥25% reduction from baseline in glucose AUC and was conducted in the modified intent-to-treat population (n=25); 15 of 25 patients (60%) were treatment responders (95% CI: 39%, 78%) and were found to have a mean A1c reduction of 1.1% at 24 weeks. As for the hypertension cohort, there were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21). Participants in the study showed varying degrees of improvement in Cushing's syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight.

XVIII. The overall quality of evidence for mifepristone (Korlym) is considered low due to open-label study design, small sample size, lack of an active or meaningful comparator, high attrition rate, and absence of a statistically significant different in the hypertension cohort. While reduction in glucose AUC is a clinically meaningful, objective endpoint correlated with improvement of hypercortisolism in Cushing's syndrome, concerns listed above limit confidence that medication is providing a clinically meaningful benefit over available treatments for Cushing's syndrome. In clinical trials for Signifor, Isturisa, and Recorlev, metabolic lab values, including glucose, were evaluated as secondary outcomes with improvements in glucose lowering, blood pressure, and weight. Close monitoring for severe hypokalemia, clinical signs of adrenal insufficiency, and QT prolongation may limit the use of mifepristone in clinical practice.

XIX. Mifepristone (Korlym) has not been evaluated against generic mifepristone for the treatment of hyperglycemia secondary to hypercortisolism in Cushing's syndrome, therefore comparative safety and efficacy remain uncertain. However, the chemical entity in generic mifepristone tablets is the same as mifepristone (Korlym) therefore, both products are expected to produce a similar efficacy and safety profile for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome, even in the absence of an FDA-labeled indication for mifepristone. Documentation of medical necessity for mifepristone (Korlym) is required, as the recommended dose can be obtained with the generic mifepristone, providing a significant price differential (6 – 10x difference). Medical necessity for mifepristone (Korlym) is limited to members that have a documented serious intolerance (e.g., allergy reaction, serious adverse event, life-threatening reaction that required hospitalization) or treatment failure with generic oral mifepristone. If a member has a contraindication to mifepristone, it is presumed that treatment with mifepristone (Korlym) would also be contraindicated, given similar warnings and side effect profile.

Investigational or Not Medically Necessary Uses

I. The agents referenced in this policy have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Exogenous (Iatrogenic) Cushing's syndrome
      i. The treatment of Cushing's syndrome due to exogenous therapy is to stop the glucocorticoid. Safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) has only been established for endogenous Cushing's (e.g. ACTH dysregulation caused by tumor, etc), there is currently limited evidence to suggest the use of the agents in this policy in the setting of exogenous (iatrogenic) Cushing's syndrome.
   B. Agents in the policy used in combination
      i. Approved treatments are not to be used in combination with other specialty medications listed in this policy used to treat Cushing's given lack of scientific evidence to safely recommend their use as dual therapy. Sufficient data is not currently available to support the safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) use in combination with other agents listed in these criteria. Osilodrostat (Isturisa) and Pasireotide diaspartate (Signifor) have not been studied in

combination with one another or with agents used for Cushing's syndrome (levoketoconazole (Recorlev) and/or mifepristone (Korlym), etc.). Levoketoconazole (Recorlev) has not been studied in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), or mifepristone (Korlym).

ii. In practice, ketoconazole has been used in combination with metyrapone or osilodrostat to maximize cortisol level lowering when monotherapy has been ineffective; triple therapy (ketoconazole/pasireotide/cabergoline and ketoconazole/metyrapone/mitotane) has also been used in patients with uncontrolled cortisol levels and presence of visible tumor post-resection. However, quality of evidence supporting combination use is low and there are significant safety concerns due to additive toxicity (QT prolongation, hepatotoxicity).

C. Acromegaly
    i. Pasireotide diaspartate (Signifor) subcutaneous syringe does not carry an FDA approval in the setting of acromegaly; however, Pasireotide pamoate (Signifor LAR) product is approved in this setting. Notably, coverage of pasireotide pamoate (Signifor LAR) under the pharmacy benefit is excluded due to provider administration exclusion. Other somatostatin agents used in acromegaly include Sandostatin LAR, Sandostatin, and somatuline.
D. Pancreatic fistula, postoperative; prophylaxis
    i. Limited data evaluating pasireotide diaspartate (Signifor) demonstrated reduction in relative risk only, therefore use of pasireotide diaspartate (Signifor) for prophylaxis or postoperative treatment of pancreatic fistula is considered experimental and investigational.
E. Carcinoid syndrome
    i. Pasireotide diaspartate (Signifor) failed to demonstrate statistically significant benefit for the treatment of carcinoid syndrome. Additionally, use is not recognized by NCCN guidelines, therefore use of pasireotide diaspartate (Signifor) for carcinoid syndrome is considered experimental and investigational.
F. Neuroendocrine tumor (NETS)
    i. Pasireotide diaspartate (Signifor) failed to improve symptom control or tumor response in clinical trials evaluating treatment for NETS. Additionally, use is not recognized by NCCN guidelines, therefore use pasireotide diaspartate (Signifor) for NETs is considered experimental and investigational.
G. Vasoactive intestinal peptide tumors (VIPomas) [pancreatic neuroendocrine (islet cell) tumor, insulinoma, glucagonoma, somatostatinoma, and gastrinoma]
    i. Pasireotide diaspartate (Signifor) failed to improve symptom control or tumor response in clinical trials evaluating treatment for VIPoma. Additionally, use is not recognized by NCCN guidelines, therefore use pasireotide diaspartate (Signifor) for VIPoma is considered experimental and investigational. Appropriate treatment options may include injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen).
H. Treatment of fungal infections

i. Safety and efficacy of levoketoconazole (Recorlev) has not been established for treating fungal infections and should not be substituted for ketoconazole when used to treat fungal infections. Additionally, drugs or interventions that a treating licensed health care provider recommends are considered medically necessary if the level of service, intervention, or prescription drug recommended for the condition is cost-effective compared to alternative interventions. Therefore, it is considered not medically necessary.

I. Type 2 diabetes unrelated to endogenous Cushing's Syndrome
    i. Safety and efficacy of mifepristone (Korlym) has only been established for hyperglycemia secondary to hypercortisolism in members with endogenous Cushing's syndrome; therefore, hyperglycemia due to type 2 diabetes alone is considered experimental and investigational.

J. Hypertension associated with Cushing's syndrome
    i. In the SEISMIC clinical trial evaluating mifepristone, the hypertension cohort demonstrated no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21). Therefore, use of mifepristone is considered not medically necessary for any symptoms outside of hyperglycemia (e.g. hypertension, weight loss, cortisol induced-psychosis) related symptoms secondary to hypercortisolism.

K. Termination of pregnancy and induction of labor
    i. Although the active ingredient, mifepristone, at a lower strength is indicated for both termination of pregnancy and induction of labor, mifepristone (Korylm) has not been approved by the FDA or studied in those indications. Therefore, mifepristone (Korylm) is considered not medically necessary.

Appendix

I. Levoketoconazole (Recorlev)
    A. The recommended initial dosing of levoketoconazole is 150 mg twice daily and dosing is titrated by 150 mg daily every 2-3 weeks until an adequate clinical response is achieved based on cortisol levels and patient tolerability. The maximum recommended dosage is 1,200 mg per day in divided doses.
    B. Levoketoconazole (Recorlev) carries black box warning for hepatotoxicity and is contraindicated in patients with cirrhosis, elevated LFT defined as baseline AST or ALT > 3 times the upper limit of normal, acute liver disease or poorly controlled chronic liver disease, extensive metastatic liver disease, or recurrent symptomatic cholelithiasis. Cases of serious hepatoxicity were reported in patients taking levoketoconazole (Recorlev) and therefore treatment with levoketoconazole (Recorlev) is contraindicated in patients with a prior history of drug induced liver injury with ketoconazole or any azole antifungal therapy that required treatment discontinuation (serious and fatal hepatotoxicity have been reported in patients taking oral ketoconazole). Baseline liver function tests should be obtained prior to starting therapy and continuously monitored throughout treatment.
    C. Levoketoconazole (Recorlev) also carries a black box warning for QT prolongation and is contraindicated with other drugs that prolong the QT interval, in patients with a

prolonged QTcF interval of greater than 470 msec at baseline, and in patients with a history of torsade's de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history). A baseline electrocardiogram (ECG) function test should be obtained prior to starting therapy.

References

1. Isturisa [Prescribing Information]. Recordati Rare Disease, Inc: Lebanon, NJ USA 08833. March 2020.
2. Signifor injection [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2020.
3. Recorlev [Prescribing Information]. Xeris Pharmaceuticals, Inc: Chicago, IL. December 2021.
4. Korlym [Prescribing Information]. Menlo Park, CA: Corcept Therapeutic, Inc. November 2019.
5. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847-875. doi:10.1016/S2213-8587(21)00235-7
6. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831. doi:10.1210/jc.2015-1818
7. Nieman LK, Biller BMK, Findling JW, et al. The diagnosis of Cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540.
8. American Association of Neurological Surgeons. Cushing's Syndrome/Disease. (n.d.). Retrieved February 14, 2022, from https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Cushings-Disease
9. Colao A, Petersenn S, Newell-Price J, et al. A 12-month phase 3 study of pasireotide in Cushing's disease [published correction appears in N Engl J Med. 2012 Aug 23;367(8):780]. *N Engl J Med*. 2012;366(10):914-924. doi:10.1056/NEJMoa1105743
10. Vitale G, Dicitore A, Sciammarella C, et al. Pasireotide in the treatment of neuroendocrine tumors: a review of the literature. *Endocr Relat Cancer*. 2018;25(6):R351-R364. doi:10.1530/ERC-18-0010
11. Lacroix A, Gu F, Schopohl J, et al. Pasireotide treatment significantly reduces tumor volume in patients with Cushing's disease: results from a phase 3 study. *Pituitary*. 2020;23(3):203-211. doi:10.1007/s11102-019-01021-2
12. Pivonello R, Fleseriu M, Newell-Price J, et al. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase [published correction appears in Lancet Diabetes Endocrinol. 2020 Aug 5;:]. Lancet Diabetes Endocrinol. 2020;8(9):748-761. doi:10.1016/S2213-8587(20)30240-0
13. Gadelha M, Bex M, Feelders RA, et al. Randomized trial of osilodrostat for the treatment of Cushing disease. *J Clin Endocrinol Metab.* 2022;107(7):e2882-e2895. doi:10.1210/clinem/dgac178
14. Fleseriu M, Pivonello R, Elenkova A, et al. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial [published correction appears in Lancet Diabetes Endocrinol. 2019 Nov;7(11):e22]. *Lancet Diabetes Endocrinol*. 2019;7(11):855-865. doi:10.1016/S2213-8587(19)30313-4
15. Zacharieva SZ, Pivonello R, Elenkova A, et al. Mon-332 safety and efficacy of levoketoconazole in the treatment of endogenous cushing's syndrome (Logics): a double-blind, placebo-controlled, withdrawal study. *Journal of the Endocrine Society*. 2020;4(Supplement_1):MON-332.
16. Scaroni C, Zilio M, Foti M, et al. Glucose metabolism abnormalities in Cushing syndrome: from molecular basis to clinical management. *Endocrine Reviews*, Volume 38, Issue 3, June 2017, Pages 189–219. https://doi.org/10.1210/er.2016-1105.
17. Yuen KCJ, Williams G, Kushner H, Nguyen D. Association between mifepristone dose, efficacy, and tolerability in patients with Cushing syndrome. *Endocr Pract*. 2015;21(10):1087-1092.
18. Fleseriu M, Biller BMK, Findling JW, Molitch ME, Schteingart DE, Gross C; for SEISMIC Study Investigators. Mifepristone, a glucocorticoid antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 2012;97(6):2039-2049.
19. Neiman, LK. Medical therapy of hypercortisolism (Cushing's syndrome). In: Post TW, ed. UpToDate. UpToDate; August 29, 2022. Accessed January 17, 2023. www.uptodate.com
20. Newell-Price J, Pivonello R, Tabarin A, et al. Use of late-night salivary cortisol to monitor response to medical treatment in Cushing's disease. *Eur J Endocrinol.* 2020;182(2):207-217. doi:10.1530/EJE-19-0695

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
octreotide (Sandostatin, Bynfezia Pen, Mycapssa)	Acromegaly
	Metastatic carcinoid tumor
	Vasoactive intestinal peptide tumor (VIPoma)
pegvisomant (Somavert)	Acromegaly

Policy Implementation/Update

Action and Summary of Changes	Date

Created new Cushing's Syndrome Policy, combining Isturisa, Signifor, Recorlev, and Korlym policies: Added criteria to avoid combination Cushing's agent use in initial and renewal. Updated E/I (added VIPoma), supporting evidence, references. Added related policies.
• Isturisa policy
  ○ Removed documentation of baseline UFC level.
• Korlym policy
  ○ Updated from trial of 2 to trial of all generic available agents in Cushing's, including generic mifepristone and trial of Signifor. Require documentation of medical necessity for generic mifepristone in renewal criteria.
	02/2023

Previous reviews
• Pasireotide diaspartate (Signifor)
  ○ Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated the example for improvement or stability of disease symptoms
  ○ Removal of UFC 24-hour urinary free cortisol level (UFC). Addition of age requirement and addition of previous trial of ketoconazole, metyrapone, or mitotane.
• Mifepristone (Korlym)
  ○ Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated renewal language to reflect new standard language. Updated supporting evidence.
  ○ Transitioned criteria to policy with the following updates: defined surgery in the policy, removed pregnancy question, addition of supporting evidence, and addition of investigational diagnoses along with supporting evidence.
	08/2020
	12/2019
	08/2020
	10/2019

Policy created • Levoketoconazole (Recorlev) • Osilodrostat (Isturisa) • Pasireotide diaspartate (Signifor) • Mifepristone (Korlym)	03/2022 07/2020 07/2013 09/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP050

Split Fill Management* [Applies to abemaciclib (Verzenio) ONLY]

Description

Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) are orally administered cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors, which suppress the activity of CDK 4/6 enzymes in tumor cells leading to the inactivation of certain tumor suppressor genes.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
abemaciclib (Verzenio)	Breast cancer, HER2-negative, HR-positive, advanced or metastatic; early-stage breast cancer	50 mg tablets	56 tablets/28 days
		100 mg tablets	
		150 mg tablets	
		200 mg tablets	
palbociclib (Ibrance)	Breast cancer, HER2-negative, HR-positive, advanced or metastatic	75 mg capsules/tablets	21 capsules or tablets/28 days
		100 mg capsules/tablets	
		125 mg capsules/tablets	
ribociclib (Kisqali)	Early-stage breast cancer	200 mg tablet dose pack	21 tablets/28 days
		400 mg tablet dose pack	42 tablets/28 days
	Breast cancer, HER2-negative, HR-positive, advanced or metastatic	200 mg tablet dose pack	21 tablets/28 days
		400 mg tablet dose pack	42 tablets/28 days
		600 mg tablet dose pack	63 tablets/28 days

Initial Evaluation

I. **Abemaciclib (Verzenio), palbociclib (Ibrance), or ribociclib (Kisqali)** 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. Member has <u>not</u> previously progressed on, or after, treatment with another cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor[e.g., ribociclib (Kisqali), abemaciclib (Verzenio), palbociclib (Ibrance)]; **AND**
   D. Member has a diagnosis of hormone receptor-positive (HR+) and human epidermal growth factor-negative (HER2-) breast cancer; **AND**
   E. The request is for **adjuvant therapy of early-stage (stage II-III) breast cancer (EBC)**; **AND**
      1. The member has undergone definitive surgical resection of the primary tumor; **AND**

2. The member has received or completed therapy using one of the following treatment modalities:
    i. Endocrine-based therapy (e.g., fulvestrant, tamoxifen, letrozole, anastrozole, exemestane, etc.); **OR**
    ii. Radiotherapy; **OR**
    iii. Taxane (e.g., docetaxel, paclitaxel) and/or anthracycline (e.g., doxorubicin) based chemotherapy; **AND**
3. The request is for abemaciclib (Verzenio); **AND**
    i. Abemaciclib (Verzenio) will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or tamoxifen; **AND**
    ii. Treatment will not be used in combination with any additional oncology therapy; **AND**
    iii. Provider attests the member has high-risk breast cancer based on one the following:
        a. Histopathological tests showing four or more (≥ 4) axillary lymph nodes are affected (pALN N2 or N3 disease); **OR**
        b. Histopathological tests showing one to three axillary lymph nodes are affected (N1 disease), and one of the following:
            i. Tumor size is ≥ 5 cm; **OR**
            ii. Histopathological grade 3 disease (G3); **OR**
            iii. The member has a Ki-67 score ≥ 20% as determined by an FDA-approved test; **OR**
4. The request is for ribociclib (Kisqali); **AND**
    i. Ribociclib (Kisqali) will be used in combination with an aromatase inhibitor (letrozole, anastrozole, exemestane); **OR**
    ii. Treatment will not be used in combination with any additional oncology therapy; **AND**
    iii. Provider attests the member is at high risk of recurrence; **AND**
    iv. Member has node-positive disease (N1, N2, N3); **OR**
    v. Member has no regional lymph node involvement [i.e., node-negative disease (N0)]; **AND**
        a. Tumor size ≥ 5 cm (T3-T4); **OR**
        b. Tumor size 2 – 5 cm (T2); **AND**
            i. Histopathological grade 3 disease (G3); **OR**
                1. Histopathological grade 2 disease (G2); **AND**
                    a. Member is determined to be high risk via gene expression assay (e.g., Oncotype DX Breast Recurrence Score ≥ 26; genomic profiling assays (i.e., Prosigna/PAM50, MammaPrint, or EndoPredict EPclin), etc.) or Ki-67 score ≥ 20%; **OR**

F. The request is for **advanced (stage III) or metastatic breast cancer (stage IV)**; **AND**
    1. The medication is prescribed as a first line therapy; **AND**
        i. Treatment will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or fulvestrant (Faslodex); **AND**

ii. The member is postmenopausal or receiving hormone suppression (e.g., surgical ablation, suppression with gonadotropin-releasing hormone (GnRH) therapy [e.g., leuprolide], etc.); **AND**
iii. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali); **AND**
    a. Medication will not be used in combination with any additional oncology therapy; **OR**
iv. The request is for palbociclib (Ibrance); **AND**
    a. Medication will not be used in combination with any additional oncology therapy; **AND**
        i. Documentation that treatment with abemaciclib (Verzenio)* or ribociclib (Kisqali)* is contraindicated or not tolerated; **OR**
    b. The request is for palbociclib (Ibrance) in combination with inavolisib (Itovebi)* and fulvestrant (Faslodex); **AND**
        i. Documentation of *PIK3CA* mutation; **AND**
        ii. Member has not previously progressed on a *PIK3CA* active agent (e.g., alpelisib [Piqray], capivasertib [Truqap]); **AND**
        iii. Breast cancer is endocrine resistant, defined by disease progression on, or within, 12 months of completing adjuvant therapy (e.g., letrozole, anastrozole, exemestane, tamoxifen); **AND**
        iv. Medication will not be used in combination with any other oncology therapy except for fulvestrant (Faslodex) and inavolisib (Itovebi)*; **OR**

2. The medication is prescribed as second line therapy; **AND**
    i. Treatment will be used in combination with fulvestrant (Faslodex); **AND**
    ii. Will not be used in combination with any additional oncology therapy; **AND**
    iii. The member had disease progression on, or after primary endocrine therapy (as adjuvant or first-line systemic therapy); **AND**
    iv. The member is postmenopausal or receiving hormone suppression (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **AND**
        a. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali); **OR**
        b. The request is for palbociclib (Ibrance); **AND**
            i. Documentation that treatment with abemaciclib (Verzenio)* or ribociclib (Kisqali)* is contraindicated or not tolerated; **OR**
3. The medication is prescribed as third line or later therapy in the metastatic (stage IV, M1) setting; **AND**
    i. Member had disease progression on, or after, endocrine therapy and systemic chemotherapy (not containing a cyclin-dependent kinase 4/6 [CDK 4/6] inhibitor) in the metastatic (stage IV) setting; **AND**
    ii. The request is for abemaciclib (Verzenio) monotherapy

**Please note: medications notated with an asterisk may require additional review.*

II. Abemaciclib (Verzenio), palbociclib (Ibrance) and ribociclib (Kisqali) are considered investigational when used for all other conditions, including but not limited to:
   A. In combination with, or following progression on or after, another cyclin-dependent kinase 4/6 (CDK 4/6 inhibitor) (e.g., ribociclib [Kisqali], abemaciclib [Verzenio], palbociclib [Ibrance])
   B. Ribociclib (Kisqali) or abemaciclib (Verzenio) in combination with inavolisib (Itovebi)
   C. Pancreatic neuroendocrine tumors (pNET)
   D. Ovarian or endometrial cancer
   E. Central nervous system cancers (e.g., glioma, astrocytoma, head and neck, etc.)
   F. Colorectal cancer
   G. Urothelial or renal cell carcinoma
   H. Leukemias and lymphomas
   I. Non-small-cell lung cancer
   J. Liposarcoma
   K. Biliary tract carcinoma
   L. Head and neck 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 will not be used in combination with any other oncolytic medication with the exception of an aromatase inhibitor (e.g., anastrozole, letrozole) or estrogen receptor antagonist (e.g., tamoxifen, fulvestrant (Faslodex) or palbociclib (Ibrance) in combination with inavolisib (Itovebi)* and fulvestrant (Faslodex); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., decrease in tumor size, or tumor spread)

Please note: medications notated with an asterisk may require additional review.

Supporting Evidence

I. Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) were not studied in patients under 18 years of age; therefore, their efficacy and safety in the pediatric population is unknown.
II. Many treatment options exist for advanced and metastatic breast cancer. Initial and subsequent therapies in this setting are contingent upon patient specific characteristics. Given the complexities surrounding the diagnosis and treatment options, targeted drug therapies such as cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors should be prescribed by, or in consultation with, an oncologist.
III. **Abemaciclib (Verzenio):** Abemaciclib (Verzenio) was evaluated as an early-stage adjuvant therapy, first-line or subsequent-line systemic chemotherapy in adult, female subjects with HR+,

HER2-, advanced or metastatic breast cancer. The following studies were pivotal trials for the approved indications:

a. MONARCH-E: Abemaciclib (Verzenio) was studied in the setting of adjuvant therapy for early-stage breast cancer with high risk of recurrence or metastasis, in an open-label, randomized, phase 3 trial (MONARCH-E) in 5,637 patients. Efficacy and safety of adding abemaciclib (Verzenio) to endocrine therapy (aromatase inhibitor or tamoxifen) was compared with conventional endocrine therapy. Abemaciclib (Verzenio) was administered for 2 years following a definitive tumor reduction surgery and chemotherapy with taxane and/or anthracycline in adjuvant or neoadjuvant setting. High risk was defined based on the following key factors: ≥ 4 pALN disease; or 1 to 3 positive ALN in the setting of a tumor of at least 5 cm or larger, or histologic grade 3 disease. A Ki-67 index ≥ 20% in untreated breast tissue as determined by an FDA approved test was required as a marker for high-risk of recurrence (Ki-67 is a cancer antigen protein and serves as a marker for tumor cell mitosis). Invasive disease-free survival (IDFS) was the primary endpoint. A pre-specified analysis reflecting a median follow-up of 4.5 years was published October 2023. All patients have completed the abemaciclib (Verzenio) treatment course, with more than 80% of patients having been followed for at least two years after completion. In the intent-to-treat (ITT) population, the risk of developing invasive disease was reduced by 32% (HR=0.680, 95% CI (0.599- 0.772); p<0.001). The absolute increase in invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) continued to deepen in magnitude at five years, to 7.6% and 6.7%, respectively, reflecting improvements from the two-, three-, and four-year rates. With the majority of the IDFS events being DRFS events, the DRFS benefit was also maintained with abemaciclib (Verzenio) reducing the risk of developing distant recurrence or death by 32.5% (HR=0.675, 95% CI (0.588 - 0.774); p<0.001). While overall survival (OS) data remain immature, fewer deaths were observed in the abemaciclib (Verzenio) arm (208 [7.4%] of 2,808 patients) compared to the control arm (234 [8.3%] of 2,829 patients) (HR=0.903, 95% CI (0.749- 1.088); p = 0.284). Nearly twice as many patients receiving ET alone (n=269) developed and are living with metastatic disease compared to those receiving Verzenio (n=138).
    i. As of March 2023, the FDA removed the Ki-67 testing requirement for adjuvant abemaciclib as the benefit of adjuvant use was demonstrated regardless of Ki-67 status, which allows more patients with high-risk, HR+, HER2-negative early breast cancer to be eligible for treatment.

b. MONARCH 3: Abemaciclib (Verzenio) in combination with an aromatase inhibitor. The trial evaluated postmenopausal women and with no prior systemic therapy, and was a randomized, double-blinded, placebo-controlled trial. Premenopausal women were administered GnRH therapy for at least two weeks prior to initiation of therapy for ovarian suppression and continued throughout the trial. The primary efficacy outcome was Progression-Free Survival (PFS), which favored abemaciclib (Verzenio). A secondary outcome was objective response rate (ORR), which also favored abemaciclib (Verzenio). The final OS analysis (at data cut off September 2023) resulted in longer OS in abemaciclib (Verzenio) compared to aromatase inhibitor however statistical significance was not reached. The observed improvement in median OS was 13.1 months (66.8 for

abemaciclib + aromatase inhibitor vs. 53.7 placebo + aromatase inhibitor (HR 0.804 (95%CI 0.637 – 1.015; p=0.0664)).

c. MONARCH 2: Abemaciclib (Verzenio) in combination with fulvestrant. The trial evaluated subjects with disease progression on or after adjuvant metastatic endocrine therapy, and was a randomized, placebo-controlled trial. The primary and secondary outcomes mirror that of MONARCH 3, in favor of abemaciclib (Verzenio); however, OS data was not mature at time of FDA-approval.
    i. At the final interim data cut-off reported in 2020, the ITT population (n=446) analysis reported median OS of 46.7 months for abemaciclib (Verzenio) plus fulvestrant and 37.3 months for placebo plus fulvestrant (HR= 0.757; 95% CI, 0.606-0.945; P = 0.01). Improvement in OS was consistent across all stratification factors. Among stratification factors, more pronounced effects were observed in patients with visceral disease (HR 0.675; 95%CI, 0.511-0.891) and primary resistance to prior ET (HR 0.686; 95%CI, 0.451-1.043). Time to second disease progression (median, 23.1 months vs 20.6 months) was also statistically significantly improved.
    ii. MONARCH 1: Abemaciclib (Verzenio) administered as a monotherapy in metastatic breast cancer. The trial, a single-arm, open-label, phase II trial, evaluated women who received prior endocrine therapy and one-to-two lines of chemotherapy in the metastatic setting. The primary outcomes were ORR and median duration of response (DOR). Abemaciclib (Verzenio) induced partial response in 19.7% and demonstrated an ORR of 19.7% (95% CI: 13.3–27.5). Median PFS was 6 months (95% CI: 4.2–7.5). At the final analysis, at 18 months, median OS was 22.3 months (95% CI: 17.7–not reached).
    iii. postMONARCH: Designed to show the benefit of continued treatment with CDK4/6 inhibitor therapy for patients (N=182) with HR+/HER2− advanced breast cancer that progressed or recurred after previous CDK4/6 inhibitor therapy. In postMONARCH, 182 patients were treated with (abemaciclib) Verzenio plus fulvestrant, and 186 patients were treated with placebo plus fulvestrant. The primary endpoint was investigator-assessed PFS; key secondary endpoints included PFS by blinded independent central review (BICR), OS, and ORR. Results from the primary analysis of postMONARCH with 258 events were presented at ASCO 2024. PFS rates at 6 months were 50% in the Verzenio-plus-fulvestrant arm and 37% in the placebo-plus-fulvestrant arm (HR, 0.73, 95% CI, 0.57–0.95). BICR-assessed PFS rates at 6 months were 68% in the Verzenio-plus-fulvestrant arm and 45% in the placebo plus-fulvestrant arm (HR, 0.55; 95% CI, 0.39–0.77). The investigator-assessed ORR was 17% in the Verzenio-plus-fulvestrant arm and 7% in the placebo-plus fulvestrant arm, and the BICR-assessed ORRs were 23% and 8%, respectively. Prespecified subgroup analysis showed a PFS benefit favoring Verzenio plus fulvestrant:
        1. Patients on a prior CDK4/6 inhibitor for <12 months: HR, 0.80; 95% CI, 0.50–1.29.
        2. Patients on a prior CDK4/6 inhibitor for ≥12 months: HR, 0.70; 95% CI, 0.52–0.94.

3. A consistent effect was seen across major clinical and genomic subgroups, including patients with baseline ESR1 or PIK3CA mutations.

IV. **Palbociclib (Ibrance):** Palbociclib (Ibrance) was evaluated as a first-line or subsequent-line systemic chemotherapy in adult male and female subjects with HR+, HER2-, advanced or metastatic breast cancer. The following studies were trials have evaluated the safety and efficacy of palbociclib (Ibrance) for the approved indications:

a. PALLAS: Prospective, randomized, phase III trial evaluated patients with HR+/HER- early breast cancer were randomly assigned to receive 2 years of palbociclib (Ibrance) with adjuvant endocrine therapy or adjuvant endocrine therapy alone (for at least 5 years). The primary end point of the study was iDFS. The study concluded the addition of adjuvant palbociclib (Ibrance) to standard endocrine therapy did not improve outcomes over endocrine therapy alone in patients with early HR+/HER2- eBC. At a median follow-up of 31 months, IDFS events occurred 8.8% patients who received palbociclib (Ibrance) plus endocrine therapy vs. 9.1% patients who received endocrine therapy alone, with similar results between the two treatment groups (iDFS at 4 years: 84.2% v 84.5%; HR= 0.96; 95% CI 0.81 to 1.14, p=0.65).

b. PALOMA-2: Palbociclib (Ibrance) plus aromatase inhibitor (letrozole) vs. placebo and letrozole in postmenopausal women receiving first-line treatment for HR+/HER2- mBC. This was a Phase III, randomized, double-blind, trial where subjects had no prior treatment in the metastatic setting. The results showed that palbociclib (Ibrance) plus letrozole resulted in an improved median PFS of 24.8 months compared to letrozole+placebo at 14.5 months (HR =0.58; 95% CI, 0.46 to 0.72; p <0.0001). The final OS analysis published June 2022 reported no significant survival benefit with palbociclib (Ibrance) plus letrozole over letrozole and placebo. After a median follow-up of 90 months, patients receiving palbociclib (Ibrance) + letrozole had numerically longer OS compared to letrozole monotherapy (median 53.9 months vs median 51.2 months), however the results were not statistically significant (HR=0.96; 95% CI: 0.78-1.18; *P*=0.3378).

c. PALOMA-3: Palbociclib (Ibrance) and fulvestrant vs. fulvestrant in pre- or post-menopausal HR+, HER2- advanced breast cancer patients, whose disease progressed on prior endocrine therapy in the adjuvant or metastatic setting. The median PFS was 9.5 months for the combination compared to 4.6 months for fulvestrant (HR= 0.46; 95% CI: 0.36 to 0.59; p< 0.0001). Key secondary endpoints were ORR and OS. ORR was achieved by 24.6% patients on palbociclib (Ibrance) + fulvestrant vs 10.9% on fulvestrant. An OS difference of 6.9 months was seen; median OS was 34.9 months with palbociclib (Ibrance) + fulvestrant vs 28.0 months with fulvestrant (HR=0.81; 95% CI: 0.64-1.03; p=0.09). At the updated non-prespecified OS analysis with a data cut off August 2020, data showed a numerical difference in median OS in favor of palbociclib (Ibrance), but did not reach statistical significance.

d. PENELOPE-B: Palbociclib (Ibrance) for 1 year was examined as adjuvant therapy in the metastatic setting in women who still had residual disease after undergoing neoadjuvant chemotherapy versus placebo. The study did not meet the primary endpoint of improved IDFS in women with HR+/HER- eBC.

e. P-REALITY X: Real-world effectiveness of 1L use of palbociclib (Ibrance) + letrozole vs letrozole monotherapy in HR+/HER2- mBC. This was an observational, retrospective analysis of electronic health records (EHRs) of 2888 postmenopausal women and men. The primary endpoint was OS. After stabilized inverse probability treatment weighting, median OS was 49.1 months among palbociclib (Ibrance) vs. 43.2 months vs letrozole (HR=0.76; 95% CI, 0.65-0.87; p<0.0001). Progression-free survival was 19.3 months vs versus 13.9 months, respectively (HR= 0.70; 95% CI, 0.62-0.78; p<0.0001).

f. INAVO120: A Phase 3, double-blind, placebo-controlled trial (n=325) studying patients with HR+/HER2-, PIK3CA mutated, endocrine resistant, locally advanced or metastatic breast cancer with progression during, or within, 12 months of completing adjuvant endocrine treatment with an aromatase inhibitor or tamoxifen, and in combination with inavolisib (Itovebi) and fulvestrant. Patients who had progressed with CDK 4/6 inhibitors in the neoadjuvant or adjuvant setting more than 12 months after finishing CDK 4/6 inhibitor therapy were included in the study (n=4). Patients receiving prior systemic therapy for metastatic breast cancer and those with HbA_{1C} >6% or diabetes were excluded. The majority of participants were female (98%), White (59%), with three or more organs with metastases (51%), secondary endocrine resistance (66%), and neoadjuvant or adjuvant chemotherapy (83%) and tamoxifen (48%) use. The primary efficacy outcome was median progression free survival (PFS) which was statistically significant and in favor of inavolisib (Itovebi), palbociclib (Ibrance), and fulvestrant (Faslodex) treatment arm (15 months) compared to placebo, palbociclib (Ibrance), and fulvestrant (Faslodex) (7.3 months), HR 0.43 (0.32-0.59), p<0.001. Median overall survival was immature at the time of data cut-off. The overall quality of the data is low due to lack of mature OS data and use of surrogate outcomes (e.g., PFS) which do not have a strong correlation with improvements in OS in metastatic breast cancer space.

V. **Ribociclib (Kisqali):** Ribociclib (Kisqali) was evaluated in adults with HR-positive, HER2-negative, early, advanced, and metastatic breast cancer.

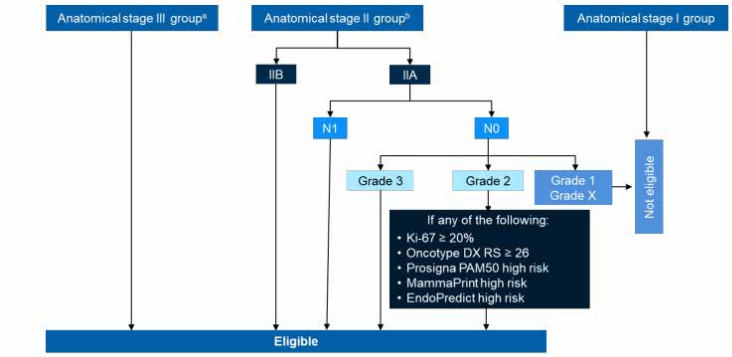
a. NATALEE: Randomized phase III, open label clinical trial comparing ribociclib (Kisqali) + nonsteroidal aromatase inhibitor (AI) as adjuvant treatment in patients with HR+/HER2- early breast cancer compared to AI alone. Patients (N=5,101) were randomized 1:1 to receive ribociclib (Kisqali) 400mg per day for 21 days on and 7 days off for 3 years along with an AI (letrozole or anastrozole) for >5 years plus goserelin in males and premenopausal females. NATALEE utilized a lower starting dose (400mg) of ribociclib than the metastatic breast cancer starting dose of 600mg to improve tolerability while maintaining efficacy. The study included patients with stage II or III disease with either lymph node–positive or –negative disease, which is a contrast to [abemaciclib] monarchE trial, which only enrolled patients with lymph node-positive disease. The primary endpoint was investigator-assessed invasive disease–free survival (iDFS) and secondary end points included recurrence-free survival (RFS), distant disease-free survival (DDFS), overall survival (OS), and safety and tolerability. At the time of the prespecified interim analysis, the median follow-up was 44.2 months, the iDFS rate was 90.8% with ribociclib (Kisqali) plus an AI vs 88.1% with an AI alone (HR = 0.715; 95% CI (0.609–0.840), P =0.0001). Findings from subgroup analyses revealed that patients with stage II (HR=0.644; 95% CI, 0.468-0.887) and stage III (HR=0.737; 95% CI, 0.611-0.888) disease

experienced an iDFS benefit with the addition of ribociclib (Kisqali) to AI. An iDFS benefit was also observed with the addition of ribociclib in patients with N0 (HR= 0.666; 95% CI, 0.397-1.118) and N1 to N3 (HR=0.731; 95% CI, 0.617-0.866) nodal status. At a median follow-up for OS of 44.3 months, the addition of ribociclib to an AI led to a reduction in the risk of death vs AI therapy alone (HR=0.827; 95% CI, 0.636-1.074; *P* = 0.0766) [follow-up for OS is still ongoing]. The 3-year regimen of ribociclib (Kisqali) at a 400-mg starting dose plus an AI was not associated with any new safety signals. Any-grade adverse effects of special interest occurring in the intervention and control arms included neutropenia (63% vs 5%), liver-related AEs (27% vs 11%), and interstitial lung disease/pneumonitis (2% vs 1%). Other clinically relevant any-grade AEs included arthralgia (39% vs 44%), nausea (24% vs 8%), headache (23% vs 17%), and fatigue (23% vs 14%).

i. As of November 2024, the NCCN guidelines for early breast cancer list ribociclib and abemaciclib as preferred category 1 recommendations for adjuvant treatment in HR+, HER2- early breast cancer at a high risk of recurrence. The NCCN further breaks down high risk of recurrence for ribociclib that mirrors the population of the NATALEE trial: patients with any lymph node involvement or if no nodal involvement either tumor size >5 cm, or if tumor size 2-5 cm, either Grade 2 (and high genomic risk or Ki-67 ≥20%), or Grade 3.

ii. While the use of these assays is not required for staging, gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. The NCCN guidelines recommend the following gene expression assays for conversation of adjuvant systemic treatment: Oncotype DX Breast Recurrence Score ≥ 26, Prosigna/PAM50, MammaPrint, or EndoPredict EPclin. The guidelines also recommend testing for Ki-67 if HR+, HER2- and considering a adjuvant CKD4/6 inhibitor.

iii. Figure 1. NATALEE Enrollment (source supplementary appendix Slamon D, Lipatov O, Nowecki Z, et al 2024)



AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or supraclavicular lymph nodes; RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm but less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growing into the chest wall or skin, includes inflammatory breast cancer.

[a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3).

[b] Capped at 40% (≈ 2000 patients). Simplified inclusion criteria are used in the illustration.

iv.

b. MONALEESA-2: Randomized, double-blind, placebo-controlled trial comparing ribociclib (Kisqali) in combination with letrozole versus placebo with letrozole in 1L

postmenopausal patients with HR/HER2- mBC. Subjects were treatment naïve for their disease. The outcomes were PFS and ORR, which were found to be statistically significant in favor of ribociclib (Kisqali) plus letrozole. Median OS data was published March 2022, showed OS 64 months with ribociclib (Kisqali) plus letrozole and 51 months with placebo plus letrozole (HR =0.76; 95% CI, 0.63 to 0.93; P = 0.008).

c. MONALEESA-7: Ribociclib (Kisqali) in combination with an aromatase inhibitor in 1L premenopausal patients. Randomized, double-blind, placebo-controlled trial of pre-perimenopausal subjects evaluating ribociclib (Kisqali) plus an aromatase inhibitor or tamoxifen with goserelin versus an aromatase inhibitor or tamoxifen and goserelin. The outcomes included PFS and ORR, which were statistically significant in favor of ribociclib (Kisqali). Overall survival data was reported in June 2019 and showed a hazard ratio (HR) of 0.712 (0.535-0.948; p=0.00973).

d. MONALEESA-3: Randomized, double-blind, placebo-controlled study of ribociclib (Kisqali) in combination with fulvestrant for 1L/2L treatment of postmenopausal women who had received zero to one line of prior endocrine therapy. This was compared to placebo plus fulvestrant. Efficacy primary outcomes were PFS and ORR which were statistically significant in favor of ribociclib (Kisqali). At 42 months, estimated survival rates among patients who received first-line therapy were 66.9% with ribociclib (Kisqali) plus fulvestrant versus 56.3% with fulvestrant alone. The median OS among patients in the early-relapse and second-line subgroup was 40.2 months with ribociclib (Kisqali) plus fulvestrant and 32.5 months with fulvestrant alone.

e. MAINTAIN: Randomized phase II trial of fulvestrant or exemestane with or without ribociclib after progression on anti-estrogen therapy plus CKD4/6i in patients with unresectable or metastatic HR+/HER2 breast cancer. The trial enrolled 120 postmenopausal women, but GnRH agonist was allow if premenopausal and/or men and less than one line of chemotherapy for metastatic breast cancer. The trial assessed PFS as the primary endpoint and ORR as a secondary endpoint. At 30 months, PFS was 5.3 vs. 2.8 for ribociclib + ET and placebo + ET, respectively (HR 0.57 (95% CI 0.39 – 0.95), p=0.006)).

VI. **Treatment of breast cancer in men:** few men have been included in breast cancer clinical trials. As such natural incidence of breast cancer in men is rare (<1%), which has also reflected in the clinical trials' sample population. Therefore, recommendations regarding management of breast cancer in men are generally extrapolated from the findings of clinical trials in women.

a. Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) have received FDA-approval in the setting of treatment of breast cancer in men. For abemaciclib (Verzenio) and ribociclib (Kisqali), this indication also extends in the adjuvant setting for the treatment of early breast cancer with high risk of recurrence.

b. Palbociclib (Ibrance) was FDA-approved for breast cancer in men in 2019. The approval was based on data from electronic health records and post marketing reports of real-world use in male patients. The sources of data included the following: IQVIA Insurance database, Flatiron Health Breast Cancer database, and the Pfizer global safety database. NCCN Guidelines recommend that men on an aromatase inhibitor and palbociclib (Ibrance) be administered a GnRH analog concurrently.

c. In the preoperative/adjuvant therapy setting, chemotherapy with or without HER2-targetted therapy is recommended in the male population. Typical adjuvant endocrine therapy options for men with breast cancer include tamoxifen, or if tamoxifen is contraindicated, an aromatase inhibitor in combination with a GnRH analog. In men, single-agent adjuvant treatment with an aromatase inhibitor has been associated with inferior outcomes compared to tamoxifen monotherapy, likely due to inadequate estradiol suppression.
d. Similarly, when aromatase inhibitor is used in combination with a CDK 4/6 inhibitor for the treatment of advanced or metastatic breast cancer in men, additional therapy with a GnRH analog (e.g., leuprolide) is recommended by NCCN guidelines for breast cancer. However, few retrospective studies involving treatment of men with metastatic breast cancer using aromatase inhibitors with or without GnRH analog showed that concurrent use of GnRH analog or type of aromatase inhibitor used did not provide statistically significant advantage in outcomes- progression free survival (PFS), and overall survival (OS).

VII. In early HR+, HER2- breast cancer, adjuvant CDK 4/6 inhibitors have been studied in high-risk patients who mostly received adjuvant/neoadjuvant chemotherapy and there are limited data in those who did not receive chemotherapy. The NATALEE trial evaluating ribociclib (Kisqali) allowed endocrine-based therapy for up to 12 months prior to randomization, being the most inclusive endocrine-based therapy eligibility window of any CDK4/6 inhibitor trial in eBC. Therefore, patients that began endocrine therapy within the last year may still be candidates for treatment with ribociclib (Kisqali). The monarchE for abemaciclib (Verzenio) allowed endocrine-based therapy for ≤12 weeks prior to randomization. In patients with germline BRCA1/2 mutation eligible for adjuvant olaparib, abemaciclib, or ribociclib, the optimal sequence of therapy and benefit is not known. In the adjuvant setting, abemaciclib (Verzenio) duration of therapy is two years, compared to three years for ribociclib (Kisqali). In absence of head-to-head trials, it is unclear whether longer CDK 4/6 inhibitor treatment in EBC may improve long-term survival and safety profiles, and patient adherence will need to be monitored in clinical practice.

VIII. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK 4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD 4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence, in combination with therapies outside of aromatase inhibitors and fulvestrant, remain unknown. The NCCN notes a lack of data to support use of an additional CDK 4/6 inhibitors after progression on a CDK 4/6 regimen. As of November 2024, the NCCN guidelines note “If there is disease progression while on palbociclib, there are limited phase II data to support the use of ribociclib in the second line setting.” However, the optimal sequencing of CDK 4/6 inhibitors is still unknown. Benefits of continuing CDK 4/6 inhibitor beyond progression remain controversial and largely unknown at this time, necessitating high quality randomized controlled trials to explore this question. PostMONARCH, a Phase 3 study, and MAINTAIN, a Phase 2 study, evaluated this question, demonstrating improved progression free survival (PFS) when abemaciclib (Verzenio) or ribociclib (Kisqali) was used after progression on CDK 4/6 inhibitors; however, overall survival data remains immature, precluding any conclusions of the impact on overall survival. The PALMIRA trial looked at continuing palbociclib (Ibrance) in the second line setting after previous progression on a palbociclib (Ibrance) based regimen.

Results demonstrated that continuing palbociclib (Ibrance) did not significantly improve PFS compared to second-line endocrine therapy alone. ELAINE 3 and EMBER 3 are other trials evaluating this question, results of which are not available at this time. Currently, there is no high-quality prospective data to suggest that continuation of CDK 4/6 inhibitor beyond initial progression is effective and more high-quality data is required before this approach can be considered standard.

IX. Endocrine therapies include, but may not be limited to, the following: tamoxifen, anastrozole, letrozole, and exemestane. Of note, the NCCN guidelines state "VTE risk should be considered when combining abemaciclib with tamoxifen." Chemotherapy regimens include, but may not be limited to, the following: doxorubicin, paclitaxel, capecitabine, gemcitabine, cyclophosphamide, carboplatin, docetaxel, cisplatin, and combinations of these therapies.

X. Postmenopausal status may be reached in women via ovarian suppression through GnRH therapy (pharmacotherapy-induced) for several weeks prior to palbociclib (Ibrance) administration, bilateral oophorectomy (surgically-induced), ovarian irradiation, or natural menopause. Any of these routes is considered acceptable for the aforementioned criteria.

XI. As of November 2024, the NCCN guidelines do not currently distinguish a preference between currently available CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) and no evidence is currently available indicating that one of these agents is superior to the other. A prospective analysis of the efficacy data of abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) as first- or second-line therapies in ER-positive advanced breast cancer noted that these agents had similar efficacy. To date, no large head-to-head comparison is currently available to support or oppose this conclusion.

Investigational or Not Medically Necessary Uses

I. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence in combination with therapies outside of aromatase inhibitors (e.g. anastrozole) and estrogen receptor antagonists (e.g. tamoxifen, fulvestrant) remain unknown. National Comprehensive Cancer Network (NCCN) acknowledges there are limited data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen.

II. There is currently no evidence supporting the use of CDK4/6 inhibitors for other types of cancer, other than the indications listed in this policy.

III. Abemaciclib (Verzenio) and ribociclib (Kisqali) received FDA approval in the setting of adjuvant therapy of high-risk early-stage breast cancer (EBC). Palbociclib (Ibrance) failed to show iDFS benefit in patients with HR+/HER2–negative early breast cancer vs. adjuvant endocrine therapy in the PALLAS and PENELOPE-B trials, therefore treatment with palbociclib in EBC is considered not medically necessary.

** 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

I. The tumor, node, metastasis (TNM) TNM system is the most common method of cancer staging in breast cancer. Numbers or letters after T, N, and M give more details about each characteristic. Higher numbers mean the cancer is more advanced.
   a. T refers to the size and extent of the main (primary) tumor.
      i. Tis: non-invasive cancer found only in ducts (carcinoma in situ)
      ii. TX: Main tumor cannot be measured
      iii. T0: Main tumor cannot be found
      iv. T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b.
   b. The N refers to the number of nearby lymph nodes involved that have cancer
      i. NX: Cancer in nearby lymph nodes cannot be measured (e.g., previously removed, etc.)
      ii. N0: There is no cancer in nearby lymph nodes
      iii. N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer
   c. The M refers to whether the cancer has metastasized
      i. MX: Metastasis cannot be measured
      ii. M0: Cancer has not spread to other parts of the body
      iii. M1: Cancer has spread to other parts of the body (distant metastasis)

II. Breast cancer is often staged before and after surgery. Clinical staging (c) is referred to staging before treatment (cTNM) and pathologic stage (p) is based on the results of tissue samples removed during surgery (pTNM).

III. Tumor grade is dependent on tumor histology. A low-grade tumor has a lower risk of recurrence. A high-grade tumor tend to grow/spread faster and have a higher risk for recurrence.
   a. GX: Grade cannot be determined
   b. G1: Low grade
   c. G2: Intermediate grade
   d. G3: High grade

IV. As of September 2024, ribociclib (Kisqali) package insert notes it should now be refrigerated before dispensing but can be stored at room temperature for up to 2 months by patients.
   a. Ribociclib (Kisqali) in advanced or metastatic breast cancer is given as 600 mg (3 x 200-mg tablets) orally, once daily (3 weeks on, 1 week off) with either an aromatase inhibitor once daily (continuously); in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines; or Fulvestrant 500 mg intramuscularly on Days 1, 15, and 29, and once monthly thereafter; in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines.
   b. In eBC, the adjuvant dosing studied was ribociclib 400-mg for 3 years.

c. If dose reduction below 200 mg/day is required, discontinue treatment

V. Abemaciclib (Verzenio) dosing
   a. Recommended starting dose in combination with fulvestrant, tamoxifen, or an aromatase inhibitor: 150 mg twice daily.
   b. Recommended starting dose as monotherapy: 200 mg twice daily.
   c. In eBC, the adjuvant dosing studied was abemaciclib 150-mg for 2 years or until disease recurrence or unacceptable toxicity
   d. Dosing interruption and/or dose reductions by 50mg may be required based on individual safety and tolerability. Discontinue ribociclib for patients unable to tolerate 50 mg twice daily.

VI. There is lack of scientific evidence from randomized controlled trials supporting the safety and/or efficacy for increased dosing or frequency of palbociclib (Ibrance). The dosing recommendation is one capsule once daily, with various doses for tolerability and dose adjustments for safety considerations, in 21 out of 28-day cycles. Increasing the dose beyond 125 mg per day or dosing more than 21 out of every 28 days has not been evaluated.

References

1. Verzenio [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company. November 2024.
2. Ibrance [Prescribing Information]. New York, NY; Pfizer Laboratories. December 2022.
3. Kisqali [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; September 2024.
4. NCCN Clinical Practice Guideline in Oncology: Invasive Breast Cancer. Version 6.2024. National Comprehensive Cancer Network. Available at https://www.nccn.org. Updated November 11, 2024.
5. Giordano SH, Freedman RA, Somerfield MR; Optimal Adjuvant Chemotherapy and Targeted Therapy Guideline Expert Panel. Abemaciclib With Endocrine Therapy in the Treatment of High-Risk Early Breast Cancer: ASCO Optimal Adjuvant Chemotherapy and Targeted Therapy Guideline Rapid Recommendation Update. *J Clin Oncol.* 2022;40(3):307-309. doi:10.1200/JCO.21.02677
6. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined With Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998. doi:10.1200/JCO.20.02514
7. Harbeck N, Rastogi P, Martin M, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. *Ann Oncol.* 2021;32(12):1571-1581. doi:10.1016/j.annonc.2021.09.015
8. Martin M, Hegg R, Kim SB, et al. Treatment With Adjuvant Abemaciclib Plus Endocrine Therapy in Patients With High-risk Early Breast Cancer Who Received Neoadjuvant Chemotherapy: A Prespecified Analysis of the monarchE Randomized Clinical Trial. *JAMA Oncol*. 2022;8(8):1190-1194. doi:10.1001/jamaoncol.2022.1488
9. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol.* 2017;35(32):3638-3646.
10. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR(+)/HER2(-) Metastatic Breast Cancer. *Clin Cancer Res.* 2017; 5218-5224.
11. Sledge GW, Toi M, Neven P, et al. The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor-Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy-MONARCH 2: A Randomized Clinical Trial. *JAMA Oncol.* 2019.
12. Sledge GW, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol*. 2017;35(25):2875-2884.
13. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial [published online ahead of print, 2022 Dec 5]. *Lancet Oncol.* 2022;S1470-2045(22)00694-5. doi:10.1016/S1470-2045(22)00694-5

14. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of ki67 in breast cancer: updated recommendations from the international ki67 in breast cancer working group. JNCI: Journal of the National Cancer Institute. 2021;113(7):808-819.
15. Polley, MY., Leung, S., Gao, D. et al. An international study to increase concordance in Ki67 scoring. *Mod Pathol.* 2015; 28, 778–786.
16. Ellis MJ, Suman VJ, Hoog J, et al. Ki67 Proliferation Index as a Tool for Chemotherapy Decisions During and After Neoadjuvant Aromatase Inhibitor Treatment of Breast Cancer: Results From the American College of Surgeons Oncology Group Z1031 Trial (Alliance). *J Clin Oncol.* 2017;35(10):1061-1069. doi:10.1200/JCO.2016.69.4406
17. Zhang A, Wang X, Fan C, Mao X. The Role of Ki67 in Evaluating Neoadjuvant Endocrine Therapy of Hormone Receptor-Positive Breast Cancer. *Front Endocrinol (Lausanne).* 2021;12:687244. Published 2021 Nov 3. doi:10.3389/fendo.2021.687244
18. Inwald EC, Klinkhammer-Schalke M, Hofstädter F, et al. Ki-67 is a prognostic parameter in breast cancer patients: results of a large population-based cohort of a cancer registry. *Breast Cancer Res Treat*. 2013;139(2):539-552. doi:10.1007/s10549-013-2560-8
19. Gil-Gil M, Alba E, Gavilá J, et al. The role of CDK4/6 inhibitors in early breast cancer. *Breast*. 2021;58:160-169. doi:10.1016/j.breast.2021.05.008
20. UpToDate. Ma C.X., Sparano J.A. Treatment approach to metastatic hormone receptor-positive, HER2-negative breast cancer: endocrine therapy and targeted agents. Updated Sept 16, 2022. Accessed November 2022.
21. UpToDate. Gradishar W.J., Ruddy K.J. Breast cancer in men. In: Post T, ed. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed December 2, 2022.
22. Gnant M, Dueck AC, Frantal S, et al. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). *J Clin Oncol.* 2022;40(3):282-293. doi:10.1200/JCO.21.02554
23. Cristofanilli M, Rugo HS, Im SA, et al. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2- ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. *Clin Cancer Res*. 2022;28(16):3433-3442. doi:10.1158/1078-0432.CCR-22-0305
24. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-The Penelope-B Trial. *J Clin Oncol*. 2021;39(14):1518-1530. doi:10.1200/JCO.20.03639
25. Martín M, Zielinski C, Ruiz-Borrego M, et al. Overall survival with palbociclib plus endocrine therapy versus capecitabine in postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer in the PEARL study. *Eur J Cancer.* 2022;168:12-24. doi:10.1016/j.ejca.2022.03.006
26. Llombart-Cussac A, Pérez-García JM, Bellet M, et al. Fulvestrant-Palbociclib vs Letrozole-Palbociclib as Initial Therapy for Endocrine-Sensitive, Hormone Receptor-Positive, ERBB2-Negative Advanced Breast Cancer: A Randomized Clinical Trial [published correction appears in JAMA Oncol. 2021 Nov 1;7(11):1729]. *JAMA Oncol*. 2021;7(12):1791-1799. doi:10.1001/jamaoncol.2021.4301
27. Mayer EL, Fesl C, Hlauschek D, et al. Treatment Exposure and Discontinuation in the PALbociclib CoLlaborative Adjuvant Study of Palbociclib With Adjuvant Endocrine Therapy for Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Early Breast Cancer (PALLAS/AFT-05/ABCSG-42/BIG-14-03). *J Clin Oncol.* 2022;40(5):449-458. doi:10.1200/JCO.21.01918
28. Bidard FC, Hardy-Bessard AC, Dalenc F, et al. Switch to fulvestrant and palbociclib versus no switch in advanced breast cancer with rising ESR1 mutation during aromatase inhibitor and palbociclib therapy (PADA-1): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2022;23(11):1367-1377. doi:10.1016/S1470-2045(22)00555-1
29. Rugo HS, Brufsky A, Liu X, et al. Overall survival with first-line palbociclib plus an aromatase inhibitor (AI) vs AI in metastatic breast cancer: a large real-world database analysis. Poster presented at European Society for Medical Oncology (ESMO) Breast Cancer 2022 Congress; May 3-5, 2022; Berlin, Germany. Poster 169P.
30. Iwata H, Im SA, Masuda N, et al. PALOMA-3: Phase III Trial of Fulvestrant With or Without Palbociclib in Premenopausal and Postmenopausal Women with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer That Progressed on Prior Endocrine Therapy-Safety and Efficacy in Asian Patients. *J Glob Oncol*. 2017;3(4):289-303.
31. Kim ES, Scott LJ. Palbociclib: A Review in HR-Positive, HER2-Negative, Advanced or Metastatic Breast Cancer. *Target Oncol*. 2017;12(3):373-383.
32. Finn R.S., Martin M., Rugo H.S., et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375(20): 1925-1936.
33. Pfizer Press Release. U.S. FDA Approves Ibrance (palbociclib) for the Treatment of Men with HR+, HER2-, Metastatic Breast Cancer. April 4, 2019. Available at: https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_ibrance_palbociclib_for_the_treatment_of_men_with_hr_her2_metastatic_breast_cancer. Access May, 2019.

34. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomized phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915.
35. Im SA, Lu YS, Bardia A, et al. Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer. *N Engl J Med.* 2019;381(4):307-316.
36. O'Shaughnessy J, Petrakova K, Sonke GS, et al. Ribociclib plus letrozole versus letrozole alone in patients with de novo HR+, HER2- advanced breast cancer in the randomized MONALEESA-2 trial. *Breast Cancer Res Treat.* 2018;168(1):127-134.
37. Slamon DJ, Neven P, Chia S, et al. Phase III Randomized Study of Ribociclib and Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472.
38. Petrelli F, Ghidini A, Pedersini R, et al. Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials. Breast Cancer Research and Treatment (2019) 174:597–604.
39. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE). *J Clin Oncol*. 2020 Dec 1;38(34):3987-3998.
40. Bystricky B, Koutek F. et al. Male breast cancer- a single center experience. *Oncol*. Lett. 2016; 12(2); 16115-1619.
41. Zagouri F, Sergentanis TN et al. Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. *Br J Cancer.* 2013 Jun 11;108(11):2259-63.
42. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med*. 2022;386(10):942-950.
43. National Cancer Institute. Cancer Staging. Available at: https://www.cancer.gov/about-cancer/diagnosis-staging/staging. Accessed December 2, 2022.
44. Ganfornina Andrades A, Fénix Caballero S, Salguero Olid A, Alegre Del-Rey EJ. Abemaciclib as adjuvant treatment for high-risk early breast cancer. [Artículo traducido] Abemaciclib en adyuvancia para el tratamiento del cáncer de mama precoz de alto riesgo. *Farm Hosp*. 2024;48(2):T75-T78. doi:10.1016/j.farma.2023.10.010
45. Kalinsky K, Bianchini G, Hamilton EP, et al. Abemaciclib plus fulvestrant vs fulvestrant alone for HR+, HER2- advanced breast cancer following progression on a prior CDK4/6 inhibitor plus endocrine therapy: Primary outcome of the phase 3 postMONARCH trial. JCO. 2024;42(17_suppl):LBA1001-LBA1001.
46. PR Newswire. Landmark 5-year monarche outcome data demonstrate verzenio (abemaciclib)'s long-term impact on cancer recurrence in high-risk early breast cancer.published October 20, 2023. https://www.prnewswire.com/news-releases/landmark-5-year-monarche-outcome-data-demonstrate-verzenio-abemaciclibs-long-term-impact-on-cancer-recurrence-in-high-risk-early-breast-cancer-301962737.html
47. Slamon D, Lipatov O, Nowecki Z, et al. Ribociclib plus endocrine therapy in early breast cancer. *N Engl J Med.* 2024;390(12):1080-1091. doi:10.1056/NEJMoa2305488Title
48. Kalinsky K, Accordino MK, Chiuzan C, et al. Randomized phase ii trial of endocrine therapy with or without ribociclib after progression on cyclin-dependent kinase 4/6 inhibition in hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: maintain trial. *J Clin Oncol*. 2023;41(24):4004-4013. doi:10.1200/JCO.22.02392

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
olaparib (Lynparza)	Early, high-risk breast cancer
everolimus (Afinitor)	Advanced breast cancer
talazoparib (Talzenna)	Locally advanced or metastatic breast cancer
Gonadotropin-releasing hormone (GnRH)	Advanced prostate cancer
	Advanced breast cancer in premenopausal women
alpelisib (Piqray, Vijoice)	Breast cancer, HR+, HER2-, PIK3CA+, advanced or metastatic
lapatinib (Tykerb)	Advanced or metastatic breast cancer
tucatinib (Tukysa)	Metastatic breast cancer
neratinib (Nerlynx)	Early breast cancer
	Advanced, metastatic breast cancer
elacestrant (Orserdu)	Breast cancer, HR+, HER2-, ESR1+, advanced or metastatic
capivasertib (Truqap)	Breast cancer, HR+, HER2-, PIK3CA/AKT1/PTEN+, advanced or metastatic

Policy Implementation/Update

Action and Summary of Changes	Date
Added a new indication for palbociclib (Ibrance) – first line treatment of metastatic or advanced breast cancer in combination with inavolisib (Itovebi) and fulvestrant (Faslodex).	02/2025
Removed Kisqali/Femara as it has been discontinued by the manufacturer. Reintroduced high-risk criteria for Verzenio in early breast cancer. Expanded criteria for high-risk disease for Kisqali in the setting of early breast cancer per NATALEE trial. Updated supporting evidence. Updated appendix. Updated related policies.	12/2024
Added expanded indication for Kisqali in the setting of early breast cancer. Removed high-risk criteria for Verzenio in early breast cancer. Added endocrine-based therapy as an adjuvant treatment option. Updated supporting evidence for monarchE trial, NATALEE trial, MAINTAIN trial. Updated references.	11/2024
Effective 01/01/2023 - Updated criteria in early breast cancer to allow coverage when Ki-67 <20% to align with definition of high-risk breast cancer NCCN/ASCO guidelines. Updated criteria requiring trial of Verzenio or Kisqali prior to Ibrance in setting of systemic therapy of recurrent, advanced, or metastatic breast cancer due to new OS data from PALOMA-2 trial. Updated criteria formatting. Updated supporting evidence and references. Added related policies and appendix.	12/2022
Updated requirement of palbociclib (Ibrance) and abemaciclib (Verzenio) prior to Kisqali to an or, in setting of systemic therapy of recurrent, advanced, or metastatic breast cancer.	10/2022
Added expanded indication for Abemaciclib (Verzenio) for adjuvant therapy of high-risk early stage breast cancer; added and rearranged relevant supporting information; updated policy to categorize adjuvant therapy for EBC vs systemic chemotherapy for advanced and metastatic breast cancer; aligned use of Verzenio and Ibrance in male population with current FDA approval and recommendations; removed specialist prescribing criteria for renewal; added split fill requirement for Verzenio	11/2021
Addition of wording related to GnRH therapy to induce menopause in order to clarify the FDA approval for Kisqali in pre/perimenopausal setting	03/2021
Transitioned criteria to policy format and merged into one policy and added add step through abemaciclib (Verzenio) and palbociclib (Ibrance) for Kisqali, effective 1/1/2021.	12/2020
Previews reviews • Verzenio: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice and removal of subgroup analysis exclusions, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); added new indication: first-line treatment in combination with an aromatase inhibitor (2018); clarified use of concomitant medication (2017) • Kisqali: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice (2019); updated product availability with Kisqali-Femara dose pack, added new indication for pre/perimenopausal setting in combination with aromatase inhibitor, as well as postmenopausal setting in combination with fulvestrant as first or second line endocrine therapy, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2018) • Ibrance: Updated QL box to inform about transition to tablets (2020), Added new indication and FDA-approval of breast cancer in men, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); updated criteria to allow treatment after disease progression on prior endocrine therapy (2016)	03/2020 10/2019 05/2019 09/2018 08/2018 03/2018 09/2017 01/2016
Criteria created • Verzenio • Kisqali • Ibrance	10/2019 04/2017 02/2015

Policy Type: PA Pharmacy Coverage Policy: UMP092

Description

Cyproheptadine is an orally administered antihistamine.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
cyproheptadine	4 mg tablets	Appetite stimulation; Migraine prophylaxis	120 tablets/30 days	005604
cyproheptadine	2 mg/5mL		1,200 mL/30 days	005603

Initial Evaluation

I. Cyproheptadine may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. Loss of appetite; **AND**
         i. Member is less than 18 years of age
      2. Headache or migraine prophylaxis; **AND**
         i. Member is less than 18 years of age; **OR**
         ii. Member is 18 years of age or older; **AND**
            a. Documentation of history of trial and failure of prophylactic therapy with at least one agent listed in each of the following groups (of note, if a group of agents is contraindicated, a trial and failure of at least three agents listed in the remaining groups is required):
               i. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
               ii. Group 2: amitriptyline, venlafaxine
               iii. Group 3: topiramate, sodium valproate, divalproex sodium; **AND**
            b. Documentation of use of each of the prophylactic therapies at therapeutic doses for at least 3 months

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

II. Cyproheptadine is considered not medically necessary when criteria above are not met and/or when used for:
   A. Use for other indications as there are over the counter alternatives for antihistamine products.

III. Cyproheptadine is considered investigational when used for all other conditions, including but not limited to:
   A. Functional abdominal pain
   B. Weight loss with cancer
   C. Combination therapy or monotherapy for ADHD
   D. Fatigue post stroke

Renewal Evaluation

I. Confirmed diagnosis of:
   A. Appetite stimulation; **AND**
      1. Documentation of treatment benefit as indicated by weight stability or gain.
   B. Migraine prophylaxis; **AND**
      1. Documentation of treatment benefit as indicated by a decrease in the number or severity of migraines.

Supporting Evidence

I. Plan covers use for appetite stimulation in pediatric population.
II. Guidelines recommend select beta blockers, antidepressants, anticonvulsants, and onabotulinumtoxinA, as efficacious or probably efficacious (Level A and B, respectively) for the prophylactic treatment of migraine in adults. If onabotulinumtoxinA has been stated, this may be used as one qualifier of the three required agents to meet payment consideration for a quantity exception. Agents not listed here have lower level, or conflicting evidence. This includes, but is not limited to SSRIs, cyproheptadine, clonidine, guanfacine, nebivolol, pindolol, carbamazepine, lisinopril, candesartan, duloxetine, calcium channel blockers, gabapentin, pregabalin, lamotrigine, oxcarbazepine, clomipramine, telmisartan, and benzodiazepines. There is limited evidence for efficacy for any class of agents for pediatric patients. Coupled with safety concerns of many of the convention migraine agents in pediatric patients, trial and failure of other conventional agents prior to coverage of cyproheptadine is not indicated at this time.
III. Guidelines label a “treatment success” as a 50% reduction in migraine after three months or prophylactic therapy utilization. Additionally, some agents take one-to-three months to begin working. If the prophylactic therapies have not been trialed for three months, this does not constitute an adequate trial of that agent. Of note, adverse effects and contraindications may limit ability to utilize an agent, or class of agents for three months, and this should be taken into consideration when determining if criteria coverage has been met.
IV. Antihistamines are not covered in adults due to over-the-counter products.

Investigational or Not Medically Necessary Uses

I. Clinical trials are ongoing for the following indications:
   A. Indication of functional abdominal pain
   B. Indication of weight loss with cancer
   C. Indication of combination therapy for ADHD
   D. Indication of fatigue post stroke.

References

1. Lewis DW, Diamond S, Scott D, Jones V. Prophylactic treatment of pediatric migraine. Headache. 2004;44(3):230-7.
2. Worawattanakul M, Rhoads JM, Lichtman SN, Ulshen MH. Abdominal migraine: prophylactic treatment and follow-up. J Pediatr Gastroenterol Nutr. 1999;28(1):37-40.
3. Watemberg NM, Roth KS, Alehan FK, Epstein CE. Central anticholinergic syndrome on therapeutic doses of cyproheptadine. Pediatrics. 1999;103(1):158-60.
4. Couluris M, Mayer JL, Freyer DR, Sandler E, Xu P, Krischer JP. The effect of cyproheptadine hydrochloride (periactin) and megestrol acetate (megace) on weight in children with cancer/treatment-related cachexia. J Pediatr Hematol Oncol. 2008;30(11):791-7.
5. Epifanio M, Marostica PC, Mattiello R, et al. A randomized, double-blind, placebo-controlled trial of cyproheptadine for appetite stimulation in cystic fibrosis. J Pediatr (Rio J). 2012;88(2):155-60.
6. Gilmore B, Michael M. Treatment of acute migraine headache. Am Fam Physician. 2011;83(3):271-80.
7. Weatherall MW. The diagnosis and treatment of chronic migraine. Ther Adv Chronic Dis. 2015;6(3):115-23.

Policy Implementation/Update:

Date Created	January 2013
Date Effective	January 2013
Last Updated	May 2018
Last Reviewed	05/2018, 06/2019

Action and Summary of Changes	**Date**
Converted to policy	06/06/2019
Criteria update: Added indication of migraine prophylaxis in pediatric patients, updated document to standard format, and updated questions to yes/no format for systematic implementation into criteria builder for Cover My Meds programming.	05/30/2018
Criteria update: Excluded samples and updated renewal language to general improvement.	1/11/2016

Cystic Fibrosis, CFTR Modulators

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP041

Description

Ivacaftor (Kalydeco) is an orally administered cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. Ivacaftor/lumacaftor (Orkambi) combines the potentiating mechanism of ivacaftor with lumacaftor which improves the conformational stability of F508del-CFTR. Ivacaftor/tezacaftor (Symdeko) includes tezacaftor, which is a CFTR modulator that acts as a CFTR corrector. Elexacaftor/tezacaftor/ivacaftor (Trikafta), adds an addition CFTR corrector with elexacaftor. Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek), improved upon the prior CFTR potentiators by including deutivacaftor, a once daily potentiator.

Length of Authorization

- Initial: Length of benefit

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ivacaftor (Kalydeco)	Cystic fibrosis, one mutation in the CFTR gene[a] that is responsive to ivacaftor[b]	150 mg tablet	56 tablets/28 days
		5.8 mg packet oral granules	56 packets/28 days
		13.4 mg packet oral granules	56 packets/28 days
		25 mg packet oral granules	56 packets/28 days
		50 mg packet oral granules	56 packets/28 days
		75 mg packet oral granules	56 packets/28 days
ivacaftor/lumacaftor (Orkambi)	Cystic fibrosis, homozygous for F508del mutation	125/200 mg tablet	112 tablets/28 days
		125/100 mg tablet	112 tablets/28 days
		94/75 mg oral granule packet	28 packets/28 days
		125/100 mg oral granule packet	56 packets/28 days
		188/150 mg oral granule packet	56 packets/28 days
ivacaftor/tezacaftor (Symdeko)	Cystic fibrosis, homozygous F508del mutation or at least one mutation in the CFTR gene[a] that is responsive to ivacaftor/tezacaftor[b]	Kit: (ivacaftor; ivacaftor/tezacaftor) 150mg; 150/100mg	56 tablets/28 days
		Kit: (ivacaftor; ivacaftor/tezacaftor) 75mg; 75/50 mg	56 tablets/28 days
	Cystic fibrosis, one F508del mutation or at least	Kit (elexacaftor/ tezacaftor/ivacaftor;	84 tablets/28 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

elexacaftor/ tezacaftor/ivacaftor (Trikafta)	mutation if the CFTR gene[a] that is responsive[b]	ivacaftor) 100/50/75mg; 150 mg	
		Kit (elexacaftor/ tezacaftor/ivacaftor; ivacaftor) 50/37.5/25mg; 75 mg	84 tablets/28 days
		Kit (elexacaftor/ tezacaftor/ivacaftor; ivacaftor) 100/50/75mg; 75mg	56 packets/28 days
		Kit (elexacaftor/ tezacaftor/ivacaftor; ivacaftor) 80/40/60mg; 59.5mg	56 packets/28 days
vanzacaftor/tezacaftor/ deutivacaftor (Alyftrek)	Cystic fibrosis, one F508del mutation or at least one mutation in the CFTR gene[a] that is responsive[b]	4mg/20mg/50mg tablet	90 tablets/30days
		10mg/50mg/125mg tablet	60tablets/30days

[a] Specific mutations listed below in policy criteria

[b] Based on clinical and/or *in vitro* assay data

Initial Evaluation

I. **Agents listed in this policy** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   B. The medication is not used in combination with other agents in this policy (i.e., use of only one of the following at a given time: Kalydeco, Orkambi, Symdeko, Trikafta, Alyftrek) (*please note: if a previous approval has been granted for one of these agents, and criteria is met for another, the previous PA approval will be discontinued)*; **AND**
   C. A diagnosis of **Cystic Fibrosis (CF)** when the following are met:
      1. For ivacaftor (Kalydeco):
         i. The member is one month of age or older; **AND**
         ii. Documentation that the member has a mutation that is eligible for treatment with ivacaftor (Kalydeco) as defined in the FDA label; **AND**
         iii. Member Gene Mutation supported by Table in Package Insert: KALYDECO® (ivacaftor); OR
      2. For ivacaftor/lumacaftor (Orkambi):
         i. The member is one year of age or older; **AND**
         ii. The member is homozygous (two copies) for the F508del mutation in the CFTR gene; **OR**
      3. For ivacaftor/tezacaftor (Symdeko):
         i. The member is six years of age or older; **AND**
         ii. The member has **ONE** of the following:

a. The member is homozygous (two copies) for the F508del mutation (*please note: one copy of F508del in the absence of a responsive mutation listed below does not meet criteria)*; **OR**
b. Documentation that the member as a mutation that is eligible for treatment with ivacaftor/tezacaftor (Symdeko) defined in the FDA label; **AND**

iii. Member Gene Mutation supported by Table in Package Insert: SYMDEKO® (tezacaftor/ivacaftor and ivacaftor); **OR**

4. For elexacaftor/tezacaftor/ivacaftor (Trikafta):
   i. The member is two years of age or older: **AND**
   ii. The member has **ONE** of the following:
      a. The patient has at least one copy of the F508del mutation; **OR**
      b. Documentation that the member as a mutation that is eligible for treatment with elexacaftor/tezacaftor/ivacaftor (Trikafta) defined in the FDA label; **AND**
   iii. Member Gene Mutation supported by Table in Package Insert: TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor); **OR**
5. For vanzacaftor/tezacaftor/deutivacaftor (Alyftrek):
   i. The member is six years of age or older; **AND**
   ii. The member has **ONE** of the following
      a. The patient has at least one copy of the F508del mutation; **OR**
      b. Documentation that the member has a mutation that is eligible for treatment with vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) defined in the FDA label; **AND**
   iii. Member Gene Mutation supported by Table in Package Insert: ALYFTREK™ (vanzacaftor/tezacaftor/deutivacaftor)

II. Medications listed in this policy are considered investigational when used for all other conditions, including but not limited to:
   A. Cystic fibrosis outside of the specific mutations listed above for each medication.
   B. Cystic fibrosis outside of ages listed above for each medication
   C. Chronic obstructive pulmonary disease and/or asthma
   D. Hyperglycemia or diabetes mellitus
   E. Premature termination codon mutations

Supporting Evidence

I. Cystic fibrosis is an autosomal recessive disease that manifests primarily with pulmonary complications and may often affect several other organ systems. Treatment and management of cystic fibrosis is complex and requires a myriad of treatment modalities. A specialist should direct, or at least be consulted, at every stage of the member's care.
II. The use of the CFTR agents has not been studied in combination with other CFTR modulators, and due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.
III. The safety of efficacy of Ivacaftor (Kalydeco) has been evaluated in several clinical trials.

- Originally approved in 2012, two trials evaluated ivacaftor (Kalydeco) in patients with G551D mutation in the CFTR gene. The primary outcome in both studies was absolute change from baseline in percent predicted pre-dose FEV1 through 24 weeks of treatment. Trial one evaluated patients 12 years of age and older (10.6%; p<0.0001), and Trial 2 evaluated patients six to 11 years of age (12.5%; p<0.0001). Additional outcomes included change in body weight, change in sweat chloride, and relative risk of pulmonary exacerbation, all of which were statistically significant.
- In 2014, efficacy and safety of ivacaftor (Kalydeco) was evaluated in patients ages six and older with R117H mutation which showed a statistically significant change from baseline in FEV1 and CFQ-R score.
- Between 2015 and 2018, the efficacy and safety of ivacaftor (Kalydeco) expanded into patients with G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, and S549R mutations. Outcomes included absolute change in percent predicted FEV1, change in body weight, and CFQ-R Respiratory Domain Score, all of which had statistically significant outcomes; although, there was much variability among the responses per mutation type. Continued rare mutations were further added in 2020.
- In April 2019, the FDA approved ivacaftor (Kalydeco) as the first CFTR modulator to treat eligible infants from six months of age. This was supported by data from the Phase 3 ARRIVAL study. This was based on 11 patients with cystic fibrosis. Furthermore, in September 2020, the FDA approved ivacaftor (Kalydeco) to treat patients four months of age and older. This was supported by a 24-week open-label cohort of the ARRIVAL trial, showing a similar safety profile to other FDA-approved age groups.
- In May 2023, the FDA approved an age expansion down to one month of age or older. This data was based on Trial 8 (ARRIVAL), a phase 3, 24-week, open-label, 2-part study that included patients one month of age or older. Oral granules were mixed with 5mL of age-appropriate soft food or liquid and administered with syringe or spoon (bottle use not recommended). The primary endpoint was safety, assessed by adverse events and clinical laboratory assessments, with secondary endpoints looking at absolute change from baseline in sweat chloride concentration at week 24. This data showed similar safety profile of those two years and older.
- Ivacaftor (Kalydeco) has not been shown to have efficacy in those with the F508del mutation or any of the following: A46D, G85E, E92K, P205S, R334W, R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X, N1303K.

IV. The efficacy and safety of ivacaftor/lumacaftor (Orkambi) has been evaluated in patients homozygous for the F508del mutation in the CFTR gene across several clinical trials.
- Trials 1 and 2 were 24-week, Phase 3, randomized, double-blind, placebo-controlled studies of patients aged 12 years and older with CF who were homozygous for the *F508del-CFTR* mutation. The primary endpoint in both trials was an absolute change in percent predicted forced expiratory volume in one second (ppFEV1) from baseline at Week 24 assessed as the average of the treatment effects at Week 16 and at Week 24. The treatment difference between ORKAMBI and placebo for the mean absolute change in ppFEV1 from baseline at Week 24 was 2.6 percentage points [95% CI (1.2, 4.0)] in Trial 1 (P=0.0003) and 3.0 percentage points [95% CI (1.6, 4.4)] in Trial 2 (P<0.0001). Additional key second endpoints were also met for

relative change in percent predicted FEV1 at week 24, absolute change in BMI at week 24 in trial 2.

- Trials 3 and 4 was an expansion in ages 6 to 12; both open-label studies assessing safety and tolerability of ivacaftor/lumacaftor (Orkambi) in younger patients with stable CF and the homozygous *F508del-CFTR* mutation. There were no new safety markers and an additional lung function measurement of precent predicted FEV1 at week 24 supported a 2.5% within group improvement.
- Trial 6 was an open-label study evaluating safety, tolerability and pharmacokinetics of patients aged 2-5 with stable CF and the homozygous*F508del-CFTR* mutation. This study reported same similar safety and tolerability in the 24 weeks as the prior studies
- Trial 7 was a similar open-label study assessing safety in those aged 1-2 with stable CF and homozygous *F508del-CFTR* mutations. No new safety signals were found in the studies' 24 weeks.

V. Ivacaftor/tezacaftor (Symdeko) has been evaluated in several trials.

- Trial 1 evaluated ivacaftor/tezacaftor (Symdeko) against placebo in patients 12 years of age and older that were homozygous for F508del, with the primary endpoint of change in FEV1 (4% vs 0% [3.1-4.8]; p<0.0001). Notable secondary outcomes included number of pulmonary exacerbations from baseline, absolute change in BMI from baseline, and change in CFQ-R Respiratory Domain Score from baseline. The change in number of pulmonary exacerbations was significantly reduced (0.65 [CI 0.48-0.88; p<0.0054).
- Trial 2 evaluated patients heterozygous for F508del and a second mutation predicted to be responsive to Ivacaftor/tezacaftor (Skydeko). Outcomes evaluated were similar to Trial 1. The change in FEV1 was 6.8 percentage point (CI 5.7-7.8; p<0.0001), while the change in CF-R Reparatory Domain Score was 11.1 points 9CI 8.7-13.6); p<0.0001).
- Trial 3 evaluated patients who were heterozygous for F508del mutation and a second mutation not predicted to be responsive to tezacaftor/Ivacaftor (Symdeko). The primary efficacy endpoint, a change in FEV1 compared to baseline, was 1.2 percentage points (CI -0.3-2.6), and was not significant. The study was terminated early.
- The efficacy of ivacaftor/tezacaftor (Symdeko) for patients aged six to 12 years was supported by data from a 24-week, open-label treatment period of 70 patients. Observations of safety were noted to be similar to that of the data available for ages 12 years and above.

VI. Elexacaftor/tezacaftor/ivacaftor (Trikafta) safety and efficacy was evaluated in the following clinical trials:

- Trial 1: 24-week, randomized, double-blind, placebo-controlled trial in patients 12 and older (n=403). Subjects had an F508del mutation and a second mutation that resulted in no CFTR protein or a CFTR protein that was nonresponsive to ivacaftor (Kalydeco) or ivacaftor/tezacaftor (Symdeko). A change of 13.8% ppFEV1 (primary endpoint) compared to placebo was seen in this trial.
- Trial 2: 4-week, randomized, double-blind, active-controlled trial in 107 patients, homozygous for F508del. A change of 10% ppFEV1 (primary endpoint) compared to Symdeko was seen in this trial.

i. Statistical and clinical improvement in sweat chloride, body mass index, and reduction in pulmonary exacerbations occurred in both trials 1 and 2.

- Trial 3: a 24-week phase 3 open label, multicenter study, enrolled 66 children ages six to 11 years old with CF who had either two copies of the *F508del* mutation or one copy of the *F508del* mutation and one minimal function mutation to evaluate safety, pharmacokinetics, and efficacy. The treatment was generally well tolerated, and safety data was similar to those 12 and older.
- Trial 4: Phase 3, 24-week, open label study which enrolled patients 2-5 years (n=75). The primary endpoint was safety and secondary endpoints looked at change in sweat chloride concentration and change in lung clearance index. Both of these showed clinical improvement and there were no new safety signals that were not seen in the rest of the clinical program for Trikafta.

VII. In a published update from 12/2020, Vertex released that the FDA approved updated CFTR gene mutations that were shown to be responsive from *in vitro* data for ivacaftor (Kalydeco), elexacaftor/tezacaftor/ivacaftor (Trikafta), and ivacaftor/tezacaftor (Symdeko). The package inserts have all been included in each drug policy section.

VIII. Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) safety and efficacy was evaluated in the following clinical trials:

- Trial 1 and 2: two identical randomized, active-controlled, double-blind Phase 3 trials (SKYLINE 102 and 103) in individuals aged 12 years and older. Patients in the SKYLINE program were either homozygous for *F508del,* or heterozygous for *F508del* with a minimal function mutation, a gating mutation, a residual function mutation, or one other *CFTR* mutation identified as responsive to elexacaftor-tezacaftor-ivacaftor (Trikafta). All 971 patients had a four-week run-in period to the trial where they received elexacaftor-tezacaftor-ivacaftor (Trikafta) every 12 hours. Following this run-in period, patients were randomized 1:1 to remain on elexacaftor-tezacaftor-ivacaftor (Trikafta) every 12 hours or vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) once daily. The primary endpoint was the absolute change in ppFEV1 at week 24.
    i. Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) was noninferior to elexacaftor-tezacaftor-ivacaftor (Trikafta) in absolute change from baseline in ppFEV1 at week 24 in both trials (SKYLINE 102: least-squares [LS] mean difference, 0.2 [95% CI, -0.7, 1.1]; *P* <.0001) and SKYLINE 103: LS mean difference, 0.2 [95% CI, -0.5, 0.9]; *P* <.0001).
    ii. Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) also significantly reduced sweat chloride levels at week 24 compared with elexacaftor-tezacaftor-ivacaftor (Trikafta) in both trials (SKYLINE 102: LS mean difference, -8.4 [95% CI, -10.5, -6.3]; *P* <.0001 and SKYLINE 103: LS mean difference, -2.8 [95% CI, -4.7, -0.9]; *P* =.0034).
- Trial 3: a single-arm, Phase 3 trial (RIDGELINE cohort) in children aged six through eleven with at least one *CFTR* mutation, including *F508del* that was responsive to elexacaftor-tezacaftor-ivacaftor (Trikafta). All patients were stable on elexacaftor-tezacaftor-ivacaftor (Trikafta) for at least 28 days before the study period began or received a four-week run in. All 78 patients received vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) once daily based on weight. The primary endpoint was safety and toxicity at the end of 24 weeks. Key secondary endpoints included change from baseline to week 24 in the ppFEV1, sweat chloride concentration.

i. Participants maintained normal baseline FEV1 % predicted (LS mean absolute change from baseline through week 24 was 0·0 percentage points [95% CI –2·0 to 1·9] with transition to received vanzacaftor-tezacaftor-deutivacaftor (Alyftrek)
ii. Participants improved upon baseline sweat chloride concentrations, average 40.4 mmol/L, by 8.6mmol/L (95%CI -11.0 to -6.3mmol/L) with vanzacaftor-tezacaftor-deutivacaftor (Alyftrek)

IX. Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek) is still being studied in RIDGELINE in two other cohorts down to one year of age.

X. For ease of policy upkeep, each medication is linked to the manufacturer website for the latest package insert to be found.

Investigational or Not Medically Necessary Uses

I. The aforementioned indications listed as experimental and investigational in Section II are currently being evaluated in clinical trials and/or have not yet shown efficacy and safety in moderate or high-quality clinical trials.

References

1. Kalydeco [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. May 2023.
2. Orkambi [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. May 2023.
3. Symdeko [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. June 2022.
4. Trikafta [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. May 2023.
5. Alyftrek [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. December 2024.
6. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. N Engl J Med. 2017. 377(21): 2013-2023. DOI: 10.1056/NEJMoa1709846.
7. Rowe SM, Daines C, Ringshausen RC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygous with Cystic Fibrosis. 377(21): 2024-2035. DOI: 10.1056/NEJMoa1709847.
8. Safety and pharmacokinetic study of lumacaftor/Ivacaftor in subjects aged 2 through 5 years with cystic fibrosis, homozygous for F508del. 2017. ClinicalTrials.gov (Identifier NCT02797132).
9. Vertex Pharmaceuticals. Gene Mutations and Their Role in Cystic Fibrosis. Available at: https://www.cfsource.com/the-gene-factor/?DSE+CFsource.com+%25282015%2529Gene+Factor++Unbranded+%2528DTP%2529+2015cf+genetics&utm_source=bing&utm_medium=cpc&utm_campaign=DSE%2520CFsource.com%2520(2015)&utm_term=cf%2520genetics&gclid=CPj28Zy8ycYCFdK3fgodOtcN8w&gclsrc=ds Accessed 7/10/2015.
10. Vertex Pharmaceuticals. [Media Release]. FDA Approves Orkambi (lumacaftor/ivacaftor) - the First Medicine to Treat the Underlying Cause of Cystic Fibrosis for People Ages 12 and Older with Two Copies of the F508del Mutation Retrieved from: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=920555 Accessed 7/10/2015.
11. Vertex Pharmaceuticals. [Media Release]. Vertex Receives U.S. Food and Drug Administration Approval of KALYDECO (ivacaftor) for Children with Cystic Fibrosis Ages 2 to 5 who have Specific Mutations in the CFTR Gene Retrieved from: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=902211 Accessed 7/10/2015.
12. A study to evaluate the safety, pharmacokinetics, and pharmacodynamics of Ivacaftor in subjects with cystic fibrosis who are less than 24 months of age and have a CFTR gating mutation. 2017. ClinicalTrials.gov (Identifier NCT02725567).
13. Quittner A, Suthoff E, Rendas-baum R, et al. Effect of ivacaftor treatment in patients with cystic fibrosis and the G551D-CFTR mutation: patient-reported outcomes in the STRIVE randomized, controlled trial. Health Qual Life Outcomes. 2015;13:93.
14. Ratjen F, Hug C, Marigowda G, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomized, placebo-controlled phase 3 trial. Lancet Respir Med. 2017;5(7):557-567.
15. Vertex Press Release, April 30, 2019. Investor Relations News and Events. FDA approved Kalydeco (ivcaftor) as first and only CFTR modulator to treat eligible infants with CF as early as six months of age. Available at:

https://investors.vrtx.com/news-releases/news-release-details/fda-approves-kalydecor-ivacaftor-first-and-only-cftr-modulator. Accessed on June 7, 2019.
16. A phase 3 study of VX-445 combination therapy in cystic fibrosis (CF) subjects heterozygous for F508del and a gating or residual function mutation (F/G and F/FR genotypes). NCT04058353. U.S. National Library of Medicine. clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04058353?term=elexacaftor+ivacaftor+tezacaftor&draw=2&rank=6.
17. VX-445/TEZ/IVA expanded access program for cystic fibrosis (CF) patients heterozygous for F508del mutation and a minimal function mutation (F/MF genotypes). NCT04058210. US. National Library of Medicine. clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04058210?term=elexacaftor+ivacaftor+tezacaftor&draw=2&rank=4
18. Vertex Press Release. FDA Approves Kalydeco as First and Only CFTR Modulator to Treat Eligible Infants with CF as Early as Four Months of Age. Accessed October 2020. Available at: https://investors.vrtx.com/news-releases/news-release-details/fda-approves-kalydecor-ivacaftor-first-and-only-cftr-modulator-0.
19. Vertex Press Release. FDA-approved CFTR mutations responsive to TRIKATA (elexacaftor/tezacaftor/ivacaftor and ivacaftor), SYMDEKO (tezacaftor/ivacaftor and ivacaftor), or KALYDECO (ivacaftor). Vertex Pharmaceuticals Incorporated. VXR-US-21-2000196 (v1.0) I 12/2020. Available at: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-fda-approvals-trikaftar
20. Vertex Press Release: Vertex Press Release: Vertex Announces U.S. FDA Approval for TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) in Children With Cystic Fibrosis Ages 6 through 11 With Certain Mutations. June 9, 2021. Available at: https://investors.vrtx.com/news-releases/news-release-details/vertex-announces-us-fda-approval-trikaftar
21. Vertex Press Release: Vertex Announces U.S. FDA Approval for ORKAMBI® (lumacaftor/ivacaftor) in Children With Cystic Fibrosis Ages 12 to <24 months. Available at: Vertex Announces U.S. FDA Approval for ORKAMBI® (lumacaftor/ivacaftor) in Children With Cystic Fibrosis Ages 12 to <24 months | Business Wire
22. Vertex Announces U.S. FDA Approval for TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) in Children With Cystic Fibrosis Ages 2 Through 5 With Certain Mutations. Available at https://news.vrtx.com/news-releases/news-release-details/vertex-announces-us-fda-approval-trikaftar-0
23. Vertex Announces U.S. FDA Approval for KALYDECO® (ivacaftor) to Treat Eligible Infants With CF Ages 1 Month and Older. Available at: https://www.businesswire.com/news/home/20230503006018/en/Vertex-Announces-U.S.-FDA-Approval-for-KALYDECO%C2%AE-ivacaftor-to-Treat-Eligible-Infants-With-CF-Ages-1-Month-and-Older
24. Heijerman HGM, McKone EF, Downey DG; VX17-445-103 Trial Group. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. Lancet. 2019 Nov 23;394(10212):1940-1948. doi: 10.1016/S0140-6736(19)32597-8. Epub 2019 Oct 31. Erratum in: Lancet. 2020 May 30;395(10238):1694. doi: 10.1016/S0140-6736(20)31021-7. PMID: 31679946; PMCID: PMC7571408.
25. Middleton PG, Mall MA, Dřevínek P, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. *N Engl J Med*. 2019;381(19):1809-1819. doi:10.1056/NEJMoa1908639

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of vanzacaftor/tezacaftor/deutivacaftor (Alyftrek) to the policy. Removal of renewal criteria as the policy is for the length of benefit.	05/2025
Updated approval duration to be for length of approval	05/2024
Updated age expansion for Kalydeco and Trikafta with new approvals. Updated supporting evidence to mirror other age expansions.	06/2023
Updated age expansion for Orkambi with new approval. Updated supporting evidence to mimic other age expansion trial data.	10/2022
Updated age for Trikafta with new FDA approval. Updated links to the PI to reflect a link to each manufacturer page	08/2021
Updated *CFTR* gene mutation indications with new *in vitro data,* adding additional attestation and PI for verification to that mutation.	02/2021
Kalydeco age requirement updated to four months of age (previous six) based on updated FDA-approval.	10/2020
New FDA-approved therapy, Trikafta, added to the policy. Grammatical changes and formatting edits.	02/2020
Criteria combined, transitioned to policy format for all medications. Added new indication for Kalydeco for ages 6 months and older. Symdeko now approved down to six years of age.	06/2019

Criteria update: New indication for Orkambi, approved in CF patients two years of age and older. New approval in CF for patients between the ages of 12 and 24 months for Kalydeco, previously approved only for 24 months and older. Criteria added to not allow concomitant use.	09/2018
Updated criteria to new format, removed question assessing liver enzymes levels, added references, added question regarding combination therapy with other CFTR modulating medications. Symdeko criteria created.	05/2018
Criteria update: Excluded samples and updated renewal language to general improvement.	01/2016
Policy created	02/2012

Cystine Depleting Agents

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP118

Description

Cysteamine bitartrate (Cystagon; Procysbi) is a cystine-depleting agent that lowers cystine levels within cells.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cysteamine IR (Cystagon)	50 mg capsule	Nephropathic cystinosis	60 capsules/30 days
	150 mg capsule		1.95 g/m^2/day
cysteamine DR (Procysbi)	25 mg DR capsule		60 capsules/30 days
	75 mg DR capsule		1.95 g/m^2/day
	75 mg DR granule packet		1.95 g/m^2/day
	300 mg DR granule packet		1.95 g/m^2/day

Initial Evaluation

Cysteamine bitartrate IR (Cystagon) is the preferred cystine-depleting agent.

- **Patients must have failed, have contraindication to, or intolerance of cysteamine bitartrate IR (Cystagon) prior to the consideration of cysteamine bitartrate DR (Procysbi).**
  - There is no prior authorization required for cysteamine bitartrate IR (Cystagon) when used for nephropathic cystinosis unless requesting above the quantity limit noted above.

I. **Cysteamine bitartrate DR (Procysbi)** may be considered medically necessary when the following criteria below are met:

A. A diagnosis of **nephropathic cystinosis** when the following are met:

1. Diagnosis has been confirmed with ONE of the following:
   i. Presence of corneal cysteine accumulation; **OR**
   ii. CTNS gene analysis; **OR**
   iii. Elevated intracellular cystine levels (>1nmol cystine/mg protein); **AND**
2. Documentation member has an intolerance or contraindication to cysteamine bitartrate IR (Cystagon); **OR**
   i. Documentation of unavoidable non-adherence to cysteamine IR (Cystagon) that prevents the achievement of optimal white blood cell (WBC) cystine levels (<1 nmol ½ cystine per mg protein); **AND**
3. Dose requested does not exceed 1.95 g per m^2 per day

II. Cysteamine bitartrate (Cystagon, Procysbi) 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., reduction in leukocyte cystine concentration]; **AND**
IV. If request is for a dose increase, the new dose does not exceed 1.95 g per m^2 per day.

Supporting Evidence

I. Cystinosis is a rare, multisystem genetic disorder caused by mutations within the CTNS gene on chromosome 17p13, which is characterized by the accumulation of cystine in different organs and tissues, increasing the potential for severe organ dysfunction. It is further classified into three forms known as infantile (nephropathic) cystinosis, late-onset (juvenile) cystinosis, and adult (benign or ocular nonnephropathic) cystinosis. Corneal cystine crystal accumulation may be present in all three types of cystinosis. Treatment of cystinosis is comprised of the amelioration of symptoms, the administration of cysteamine, and renal transplantation for those who progress to end-stage renal disease (ESRD). Ophthalmic cysteamine is prescribed to prevent corneal deposits, because the oral formulation does not reach the cornea due to absent corneal vascularization.
II. Diagnosis of cystinosis is confirmed by elevated intraleukocyte cystine content, (i.e. measuring cystine levels in polymorphonuclear leukocytes), detection of *CTNS* gene mutation, or demonstration of cystine corneal crystals by the slit lamp examination.
III. The immediate-release preparation of cysteamine bitartrate (Cystagon) is the most used formulation. The dose should be progressively increased from 10 to 50 mg/kg per day (maximum dose of 1.95 gm/m2 per day), given in divided doses every six hours. Cystine levels are measured in white blood cells once a maintenance dose is reached, this is then followed by monitoring monthly for three months, quarterly for one year, and then twice a year. Blood sampling should be obtained six hours after taking a dose of cysteamine. The goal of cysteamine therapy is to lower WBC cystine levels to an optimal target level of less than 1 nmol half-cystine/mg protein.
IV. The safety and efficacy of cysteamine bitartrate IR (Cystagon) was demonstrated in the National Collaborative Cysteamine Study (NCCS) which treated 94 children with nephropathic cystinosis with increasing doses of cysteamine HCl (mean dose 54 mg/kg/day) to attain white cell cystine levels of <2 nmol ½ cystine per mg protein 5 to 6 hours post-dose in comparison with an historical control group of 17 children who had been in the placebo group of a randomized placebo-controlled trial of ascorbic acid. The average median white cell cystine level attained during treatment in the NCCs was 1.7 ± 0.2 nmol ½ cystine per mg protein. Among cysteamine

patients, glomerular function was maintained over time despite the longer period of treatment and follow-up (up to 5 years vs. 2 years with placebo).

V. Cysteamine bitartrate (Procysbi) is a delayed-release formulation of cysteamine bitartrate (Cystagon). The delayed-release (Procysbi) formulation is dosed twice daily, while the immediate release (Cystagon) is dosed four times daily. Currently, there is insufficient evidence to support an additional adherence benefit from taking cysteamine DR (Procysbi) when considered together with the extensive increase in cost (estimated 90x increase). Additionally, in the pivotal trial for cysteamine DR (Procysbi), there was a higher incidence of adverse reactions in patients taking the delayed release product compared to patients taking immediate-release cysteamine (Cystagon).

References

1. Cystagon [Prescribing Information]. Morgantown, WV: Mylan Pharmaceuticals Inc.; August 2021.
2. Procysbi [Prescribing Information]. Novato, CA: Raptor Pharmaceuticals, Inc.; February 2022.
3. UpToDate, Inc. Cystinosis. UpToDate [database online]. Waltham, MA. Last updated March 11, 2022. Available at: http://www.uptodate.com/home/index.html.
4. National Organization for Rare Disorders. Cystinosis. Available at: https://rarediseases.org/rare-diseases/cystinosis/

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed PA for cysteamine bitartrate (Cystagon) in favor of RDx edit programming. Adjusted policy to reflect programming change. Updated supporting evidence.	02/2024
Addition of Procysbi granule packets	04/2020
Policy created	11/2019

dalfampridine ER (Ampyra®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP103

Description

Dalfampridine ER (Ampyra) is an orally administered broad-spectrum potassium channel blocker with an unknown mechanism of action for its therapeutic effect.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
dalfampridine ER (Ampyra)	Improve walking in patients with multiple sclerosis	10 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Dalfampridine ER (Ampyra)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Must be prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **multiple sclerosis** when the following are met:
      1. Member does not have a history of seizures; **AND**
      2. Member has a creatinine clearance (CrCl) >50 mL/min; **AND**
      3. Member has difficulty walking or leg weakness; **AND**
         i. Member must be able to ambulate (i.e., not wheelchair bound); **AND**
      4. Member is taking concurrent disease modifying therapy for multiple sclerosis (i.e., glatiramer acetate, dimethyl fumarate, interferon beta-1a, etc.) unless contraindicated.; **AND**
      5. If request is for brand Ampyra, documentation of treatment with generic dalfampridine ER has been ineffective, contraindicated, or not tolerated

II. Dalfampridine ER (Ampyra) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute spinal cord injury
   B. Disorder of neuromuscular transmission
   C. Alzheimer's disease, dementia
   D. Botulism
   E. Reversal of neuromuscular blockade
   F. Toxicity of calcium channel blockers

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ArrayRx administered by moda HEALTH

G. Non-ambulating members with multiple sclerosis

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 is taking concurrent disease modifying therapy for multiple sclerosis (i.e., glatiramer acetate, dimethyl fumarate, interferon beta-1a, etc.) unless contraindicated.; **AND**
IV. Member has demonstrated disease stability or improvement (e.g improvement in walking distance or speed); **AND**
V. If request is for brand Ampyra, documentation of treatment with generic dalfampridine ER has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. Multiple sclerosis (MS) is a common immune-mediated inflammatory disease of the central nervous system, and is characterized by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. However, because symptoms are non-specific and there are no clinical findings that are unique to MS, evaluation and care of patients with MS should be conducted by a specialist.
II. Dalfampridine ER (Ampyra) was studied in two randomized controlled trials that evaluated improvement in the timed 25-foot walk using percentage of timed walk responders as the primary outcome. Patients included in the clinical trials were required to be able to ambulate. Dalfampridine ER (Ampyra) had a significantly greater number of responders compared to placebo in both trials. Trial one had 42.9% vs 9.3% responders ($p<0.0001$) for dalfampridine ER (Ampyra) and placebo respectively. Trial two had 35% vs 8% responders ($p<0.0001$) for dalfampridine ER (Ampyra) and placebo respectively.
III. Dalfampridine ER (Ampyra) has only been studied in patients aged 18 years and older; therefore, safety and efficacy of dalfampridine ER (Ampyra) in the pediatric population remains undefined.
IV. Use of dalfampridine ER (Ampyra) is contraindicated in patients with a prior history of seizure and in those with a CrCl less than 50 mL/min. Seizures have been reported in patients with no history of seizure, and minor renal impairment (CrCl 51 to 80 mL/min) may increase risk of seizures. Permanent discontinuation is advised if seizures occur.
V. Dalfampridine ER (Ampyra) is typically seen as a complementary therapy to disease modifying therapy (DMT), which remains the standard of care for MS patients to prevent progression of disease. This position is supported by the Guidelines and Best Practices for Appropriate Use of Dalfampridine in Managed Care Populations published in the American Journal of Managed Care. However, multiple clinical trials and meta analyses have identified that the efficacy of dalfampridine is not dependent on DMT or any other medication. The FDA label notes that in the pivotal trials, the majority of patients (63%) were using DMT (interferons, glatiramer acetate, or natalizumab), but the magnitude of improvement in walking speed was independent

of concomitant treatment with these agents. Notably, dalfampridine has the highest utility when initiated in the early stages of MS, and thus initiation soon after diagnosis is imperative to preserve motor function and ambulation. Although there may be instances where monotherapy with dalfampridine ER (Ampyra) may be appropriate based on patient specific characteristics, the use of dalfampridine ER (Ampyra) as complementary therapy to DMT remains appropriate to ensure all facets of MS are addressed.

Investigational or Not Medically Necessary Uses

I. Dalfampridine ER (Ampyra) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
   A. Acute spinal cord injury
   B. Disorder of neuromuscular transmission
   C. Alzheimer's disease, dementia
   D. Botulism
   E. Reversal of neuromuscular blockade
   F. Toxicity of calcium channel blockers

II. Dalfampridine ER (Ampyra) was only studied in patients able to ambulate and is not indicated for non-ambulating members with multiple sclerosis

References

1. Dalfampridine ER [Prescribing Information]. Basking Ridge, NJ: Micro Labs USA, Inc. March 2019.
2. UpToDate, Inc. Symptom management of multiple sclerosis in adults. UpToDate [database online]. Waltham, MA. Updated 09/24/2019. Available at: http://www.uptodate.com/home/index.html. [Accessed 10/08/2019].
3. Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet. 2009;373(9665):732-8.
4. Goodman AD, Brown TR, Edwards KR, et al. A phase 3 trial of extended release oral dalfampridine in multiple sclerosis. Ann Neurol. 2010;68(4):494-502.
5. Goodman AD, Betoux F, Brown TR, et al. Long-term safety and efficacy of dalfampridine for walking impairment in patients with multiple sclerosis: Results of open-label extensions of two Phase 3 clinical trials. 2015, Vol. 21(10): 1322-1331.
6. Zhang E, Tian X, Li R, et al. Dalfampridine in the treatment of multiple sclerosis: a meta-analysis of randomized controlled trials. *Orphanet J Rare Dis*. (2021) 16:87.
7. Miravelle AA. Guidelines and Best Practices for Appropriate Use of Dalfampridine in Managed Care Populations. *Am J Manag Care*. 2011;17:S154-S160.
8. Baird JF, Sandroff BM, Motl RW. Therapies for mobility disability in persons with multiple sclerosis. *Expert Rev Neurother.* 2018 June; 18(6): 493-502.

Policy Implementation/Update:

Action and Summary of Changes	Date
Annual review completed. Adjusted length of initial duration to six months. Added requirement that member has difficulty walking to initial criteria and member is using in combination with DMT to renewal criteria. Updated supporting evidence.	03/2023
Added requirement to trial generic dalfampridine ER prior to branded Ampyra on continuation	05/2022
Transitioned criteria to policy	10/2019
Previous reviews	10/2011;

	05/2013; 01/2016; 11/2018;

Policy Type: PA/SP Pharmacy Coverage Policy: UMP016

Split Fill Management*

Description

Dasatinib (dasatinib; Sprycel; Phyrago) is an orally administered tyrosine kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
dasatinib (Sprycel)	20 mg tablets	Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)	90 tablets/30 days
	50 mg tablets		30 tablets/30 days
	70 mg tablets		30 tablets/30 days
	80 mg tablets		30 tablets/30 days
	140 mg tablets		30 tablets/30 days
	100 mg tablets	Chronic phase CML	30 tablets/30 days
	70 mg tablets	Gastrointestinal Stromal Tumors (GIST)	60 tablets/30 days
generic dasatinib	20 mg tablets	Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)	90 tablets/30 days
	50 mg tablets		30 tablets/30 days
	70 mg tablets		30 tablets/30 days
	80 mg tablets		30 tablets/30 days
	140 mg tablets		30 tablets/30 days
	100 mg tablets	Chronic phase CML	30 tablets/30 days
	70 mg tablets	Gastrointestinal Stromal Tumors (GIST)	60 tablets/30 days
dasatinib (Phyrago)	20 mg tablets	Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)	90 tablets/30 days
	50 mg tablets		30 tablets/30 days
	70 mg tablets		30 tablets/30 days
	80 mg tablets		30 tablets/30 days
	140 mg tablets		30 tablets/30 days
	100 mg tablets	Chronic phase CML	30 tablets/30 days
	70 mg tablets	Gastrointestinal Stromal Tumors (GIST)	60 tablets/30 days

Initial Evaluation

I. **Dasatinib (dasatinib; Sprycel; Phyrago)** may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in coordination with, an oncologist; **AND**
   B. Request is for generic dasatinib; **OR**
      1. If request is for brand Sprycel or brand Phyrago, generic dasatinib has been ineffective, not tolerated, or is contraindicated; **AND**

C. A diagnosis of one of the following:
    1. **Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL); AND**
        i. Adult member with resistance or intolerance to prior therapy; **AND**
            a. If resistance to prior TKI therapy:
                i. Member does not have BCR-ABL mutations T315I, V299L, or F317L; **OR**
        ii. Newly diagnosed pediatric member ≥1 year of age; **AND**
        iii. Used in combination with chemotherapy; **OR**
    2. **Ph+ Chronic myeloid leukemia (CML)**; **AND**
        i. Adult or pediatric member with newly diagnosed Ph+ CML in chronic phase; **OR**
        ii. Adult or pediatric member with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy; **AND**
            a. If resistance to prior TKI therapy:
                i. Member does not have BCR-ABL mutations T315I, V299L, and F317L; **OR**
    3. **Gastrointestinal Stromal Tumors (GIST); AND**
        i. BCR-ABL KD mutational status contains PDGFRA D842V mutation; **AND**
        ii. Member has tried and failed imatinib (Gleevec) AND sunitinib (Sutent) AND regorafenib (Stivarga) for the treatment of gastrointestinal stromal tumors

II. Dasatinib (dasatinib; Sprycel; Phyrago) is considered investigational when used for all other conditions, including but not limited to:
    A. Pancreatic cancer - Metastatic

Renewal Evaluation

I. No increase in the rate of disease progression while on therapy

Supporting Evidence

I. Per NCCN guidelines dasatinib (Sprycel) is not active against cells harboring the ABL mutations T315I, V299L, and F317L. Thus for patients with disease resistant to TKI therapy it becomes important to identify potential ABL mutations that may underlie the observed resistance to treatment.
II. The efficacy of Sprycel was investigated in open label trials in adult patients with Ph+ CML or Ph+ ALL whose disease was resistant to, or were intolerant to, imatinib: 1,158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The primary efficacy endpoint of major cytogenetic response (MCyR) in chronic phase CML was met in 63% of patients. The primary efficacy endpoint of major hematologic response (MaHR) in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was met in 44% of Sprycel patients by 7 years.
III. Prior therapy includes a minimum of 30 to 60 day trial of imatinib 400mg or more per day without a complete hematologic response or discontinuation of imatinib therapy due to toxicity.

Dosing may be escalated to 180 mg once daily in patients who do not achieve a hematologic or cytogenic response at the recommended dosage.

IV. In clinical trials imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

V. The approval for Sprycel for pediatric patients with Ph+ ALL was based on findings from a phase II trial (NCT01460160), which demonstrated a 3-year event-free survival (EFS) 64.1% (95% CI, 52.4%-74.7%) in 78 pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. This trial compared dasatinib (Sprycel) plus chemotherapy versus chemotherapy alone in the external historical control trial. Another TKI, Gleevec, was approved for this same patient population in 2013. There is no head-to-head study comparing Gleevec to Sprycel for Ph+ ALL in pediatric patients. The NCCN guidelines recommend all tyrosine kinase inhibitors within the same 2a recommendation.

VI. Dasatinib (Sprycel) in the setting of newly diagnosed chronic phase CML in adults was approved based on the DASISION trial (NCT00481247) an open label, randomized trial comparing Sprycel to imatinib. The primary endpoint of rate of confirmed complete cytogenetic response (CCyR) within 12 months was achieved in 76.8% of Sprycel patients versus 66.2% of imatibib patients. After 60 months follow-up, median time to confirmed complete cytogenetic response was 3.1 months in 215 Sprycel responders and 5.8 months in 204 imatinib responders.

VII. Treatment of Ph+ CML in chronic phase in pediatric patients ≥1 year of age was evaluated in two pediatric studies: an open-label, non-randomized dose-ranging trial (NCT00306202) and an open label, non-randomized, single-arm trial (NCT00777036). With a median follow-up of 4.5 years in newly diagnosed patients, the median durations of CCyR, MCyR, and major molecular response (MMR) could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off. With a median follow-up of 5.2 years in imatinib-resistant or -intolerant patients, the median durations of CCyR, MCyR, and MMR could not be estimated as more than half the responding patients had not progressed at the time of data cut-off.

VIII. In the setting of GIST, NCCN guidelines recommend following imatinib and sutinib, therapy with regorafenib (Cat 1). Regorafenib may then be followed by dasatinib (Sprycel) (Cat 2a). Dasatinib (Sprycel) is thus recommended as a fourth line agent in the setting of D842V mutation status.

IX. Dasatinib (Sprycel) has been studied in patients of various ages, ranging all the way down to 1 year old, in the treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). The COG AALL-0622 trial included patients 1-30 years of age (n=60) with Ph+ ALL that were considered at standard risk (i.e., allogenic hematopoietic stem-cell transplantation was not recommended yet). Patients were treated with an intensive chemotherapy regimen combined with dasatinib 60 mg/m2. Patients received dasatinib 60 mg/m2 continuously if they completed therapy through week 23 without dose-limiting toxicities. Results demonstrated the 3-year event-free survival (EFS) rate was 84.6% + 5.7%. There were no deaths resulting from toxicity and the combination of dasatinib plus intensive chemotherapy was found to be safe. Long term follow-up of dasatinib (Sprycel) in the treatment of Ph+ ALL was completed in various durations and chemotherapy regimens. Those studies demonstrated consistent, positive results compared to AALL-0622 regarding event-free survival (74.6%, median follow-up of 53 months). In addition, various long-term follow-up studies demonstrated similar overall survival rates (e.g., around 40%). Grade 3 and 4 adverse events observed include bleeding, pleural and/or pericardial effusions, diarrhea, infections, and elevated transaminases with none being a concern. Overall, these are lower quality trials (i.e., small population, surrogate markers); however, there is

moderate confidence in the data as there are multiple trials that overall porin in the direction of positive results.

Investigational or Not Medically Necessary Uses

I. Pancreatic Cancer Metastatic
   A. Sprycel is currently being evaluated for use in metastatic pancreatic cancer and is the subject of ongoing clinical trials. A phase 2 study of dasatinib (Sprycel) added to gemcitabine for subjects with locally-advanced pancreatic cancer (LAPC) was recently completed.

** 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. Sprycel [package insert]. Princeton, NJ. Bristol-Myers Squibb Company. December 2018
2. Trent JC,Wathen K, von Mehren M, et al. A phase IIstudy of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST) [abstract]. J Clin Oncol 2011; 29 (15_Suppl): Abstract 10006
   Demetri GD, Lo Russo P, MacPherson IR, et al. Phase Idose-escalation and pharmacokinetic study of dasatinib in patients with advanced solid tumors. Clin Cancer Res 2009; 15:6232-6240.
3. Dewaele B, Wasag B, Cools J, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. Clin Cancer Res. 2008;14(18):5749-58.
4. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomized, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):295-302.
   National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. Soft Tissue Sarcoma Version 2.2019. February 7, 2019.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added dasatinib (Phyrago)	09/2025
Added supporting evidence for dasatinib in the treatment of Ph+ ALL.	02/2025
Added generic dasatinib to the policy and required a t/f of generic dasatinib prior to use of branded product	09/2024
Updated to new format. Added new indication in pediatric patients with newly diagnosed Ph+ ALL. Added patient specific mutation assessment in the relapsed CML and ALL settings.	02/2019
Removed pregnancy question and adult only language as this is now approved for pediatric indications. Added regorafenib as an additional prior agent in GIST indication, as well as assessing patient specific mutation that received benefit in GIST in the salvage setting.	01/2018
Previous Reviews	03/2017

decitabine/cedazuridine (Inqovi™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP202

Description

Decitabine/cedazuridine (Inqovi) is an orally administered combination of DNA methylation inhibitor and cytidine deaminase inhibitor.

Length of Authorization

I. Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
decitabine/cedazuridine (Inqovi)	35/100 mg tablet	Myelodysplastic Syndrome (MDS); Chronic myelomonocytic leukemia (CMML)	5 tablets/28 days

Initial Evaluation

I. Decitabine/cedazuridine (Inqovi) 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. Decitabine/cedazuridine (Inqovi) will be used as monotherapy; **AND**
   D. Provider attests that member's bone marrow blast count is less than (<) 20%; **AND**
   E. Member has a diagnosis of **Myelodysplastic syndrome (MDS)**; **AND**
      I. Member has one of the following French-American-British (FAB) subtypes of **myelodysplastic syndrome (MDS)**:
         a. Refractory anemia; **OR**
         b. Refractory anemia with ringed sideroblasts; **OR**
         c. Refractory anemia with excess blasts; **OR**
         d. Chronic myelomonocytic leukemia (CMML); **AND**
      II. Documentation of the members International Prognostic Score (IPSS) denoting whether the member has intermediate or high risk (e.g. IPSS Intermediate-1; Intermediate-2, or high risk); **AND**
      III. Treatment with IV azacitidine (Vidaza) OR IV decitabine (Dacogen) has been ineffective, contraindicated, or not tolerated

II. Decitabine/cedazuridine (Inqovi) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute myeloid leukemia (AML)

B. Lower risk myelodysplastic syndrome (e.g. IPSS low; IPSS-R Very low, low; WPSS very low, low)
C. Refractory anemia with del(5q) abnormality
D. Chronic myelogenous leukemia (CML)
E. Acute lymphoblastic leukemia (ALL)
F. Multiple myeloma (MM)
G. Ovarian 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 response to treatment defined by complete or partial response to treatment, disease stabilization, or achieving transfusion independence

Supporting Evidence

I. Decitabine/cedazuridine (Inqovi) is FDA-approved for use in patients aged 18 years and older. Decitabine/cedazuridine (Inqovi) is a combination of DNA methylation inhibitor and cytidine deaminase inhibitor, indicated for the treatment of MDS, including previously treated and untreated, de novo and secondary MDS, and CMML.
II. Myelodysplastic syndrome is a heterogeneous disease involving ineffective, dysplastic hematopoiesis leading to cytopenias, bleeding, infections, and in one-third of patients ultimately progressing to acute AML. CMML is a related hematopoietic condition involving peripheral blood monocytosis. MDS may be classified in to seven subtypes as per French-British-American (FAB) system. Decitabine/cedazuridine (Inqovi) received FDA-approved for four of the seven subtypes, namely: refractory anemia; refractory anemia with ringed sideroblasts; refractory anemia with excess blasts; and CMML**.** Additionally, approval of decitabine/cedazuridine (Inqovi) was limited to intermediate-1 (Int-1), Int-2, and high-risk MDS according to the IPSS classification.
III. Based on symptoms at presentation (fatigue, bone pain, frequent infections, and bleeding), MDS may be misdiagnosed as other conditions such as anemia, HIV infection, autoimmune disorder or osteomyelitis. Proper diagnosis and treatment of MDS requires histochemical and cytogenetic studies; therefore, decitabine/cedazuridine (Inqovi) must be prescribed by, or in consultation with an oncologist or hematologist.
IV. The only FDA-approved therapies for Int-1, Int-2, and high-risk MDS and CMML are IV administered hypomethylating agents (HMA): azacitidine (Vidaza) and decitabine (Dacogen). Lenalidomide (Revlimid) oral capsule also has FDA approval for treatment of MDS; however, use of this drug is limited to transfusion-dependent anemia in low-risk MDS with 5q deletion. Decitabine/cedazuridine (Inqovi) tablet is the first oral HMA and provides the advantage of self-

administration for patients. Decitabine/cedazuridine (Inqovi) may be considered an alternative first-line therapy option for MDS and CMML treatment.

V. Regimens involving combination of IV administered HMA (azacitidine and decitabine) with other agents such has ruxolitinib (Jakafi), and venetoclax (Venclexta) have been studied and recommended by NCCN guidelines in the settings of MDS, CMML, and AML. Limited low quality clinical data are also available with respect to combinations of IV HMA with lenalidomide (Revlimid), vorinostat (Zolinza), phenylbutyrate or valproic acid. However, efficacy and safety of decitabine/cedazuridine (Inqovi) in combination with other drugs for the treatment of MDS and CMML has not been studied and remains unknown. Additionally, decitabine/cedazuridine (Inqovi) has not received FDA-approval for any other indications (e.g. CLL, AML).

VI. Decitabine/cedazuridine (Inqovi) was studied in two (Phase 2 ASTX727-1-B trial, and Phase 3 ASCERTAIN), open-label, randomized, crossover trials in 222 patients with Int-1 or Int-2 or high risk MDS or CMML. Patients with de novo or secondary MDS or CMML were included. Additional inclusion criteria consisted of absence of secondary hematological malignancy and a bone marrow blast count of ≤ 20% (of note, a bone marrow blast count of >20% is a parameter used in differential diagnosis of AML versus MDS). One prior cycle of decitabine or azacitidine was allowed, but no other chemotherapy within two weeks before randomization was permitted.

VII. The primary efficacy outcome was pharmacokinetic (PK) measurement of five-day exposure of oral decitabine/cedazuridine (Inqovi) vs IV decitabine, using area under the curve (AUC) during first two cycles of treatment. Decitabine/cedazuridine (Inqovi) showed comparable PK data to that of IV decitabine during cycles one and two of the treatment. For Phase 3 (ASCERTAIN) study, five-day oral/IV decitabine exposure was 98.9% (90% CI; 92.7, 105.6). Additionally, overall response rates (ORR) were reported in 60% patients across all cohorts during Phase 2 trial, with 21% patients exhibiting complete response (CR) to decitabine/cedazuridine (Inqovi).

VIII. Safety data was pooled from both studies. Reported treatment emergent adverse events (TEAE) were similar between oral and IV decitabine patient populations with neutropenia, thrombocytopenia, leukopenia, anemia, pneumonia, and sepsis as the most common. Gastro-intestinal (GI) adverse reactions were comparable between oral and IV formulations of decitabine. Thirteen (6.1%) deaths were reported during treatment period, among which, 11 (5.2%) were associated to adverse events. Overall, 30-day mortality rate was 0.5%.

IX. Decitabine/cedazuridine (Inqovi) has not been compared with IV azacitidine (Vidaza) or IV decitabine (Dacogen) in head-to-head clinical trials. The majority of the safety and efficacy data for hypomethylating agents in the MDS treatment space are rooted in the trials for the IV therapies. Approval of decitabine/cedazuridine (Inqovi) was based off of comparative pharmacokinetic exposure to decitabine between oral and IV formulations. Although this trial showed comparable efficacy and safety, there is lack of data to show superiority of the oral decitabine/cedazuridine (Inqovi) over IV decitabine (Dacogen). Weighing the safety, efficacy, cost, and clinical experience, IV therapies are considered standard and appropriate high-value treatment options for MDS and CMML and are preferred over decitabine/cedazuridine (Inqovi).

Investigational or Not Medically Necessary Uses

I. Decitabine/cedazuridine (Inqovi) has not been sufficiently studied for safety and efficacy for any other condition to date.

References

1. Steensma DP, Baer MR, Slack JL, Buckstein R, Godley LA, Garcia-Manero G, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. J Clin Oncol. 2009;27(23):3842–3848.
2. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Solé F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454–2465.
3. Garcia-Manero G. Myelodysplastic syndromes: 2015 update on diagnosis, risk-stratification, and management. Am J Hematol. 2015;90(9):832–841.
4. Garcia-Manero G, Griffiths EA, Steensma DP, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. *Blood*. 2020;136(6):674-683. doi:10.1182/blood.2019004143.
5. Garcia-Manero G, McCloskey J, Griffiths EA, Yee KWL, et al. Pharmacokinetic exposure equivalence and preliminary efficacy and safety from a randomized cross over phase 3 study (ASCERTAIN study) of an oral hypomethylating agent ASTX727 (cedazuridine/decitabine) compared to IV decitabine. *Blood.* 2019, 134 (S1), conference abstract.
6. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, et al (eds.). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD. 05 September 2019.
7. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz M, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–2405.
8. Parikh SA and Tefferi A. Chronic myelomonocytic leukemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol. 2012; 87: 611–619.
9. Decitabine and cedazuridine (Inqovi) [Prescribing Information]. Taiho Pharmaceutical Co., Ltd; Princeton NJ. July 2020.
10. National Comprehensive Cancer Network (NCCN) guidelines for myelodysplastic syndromes, V 1.2021; 09/2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Diabetic Test Strips and Glucometer

UMP POLICY

Policy Type: PA Pharmacy Coverage Policy: UMP165

Description

Test strips and meters are used to measure the concentration of glucose in the blood through a small blood draw sample from piercing the skin (typically on the finger).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Test Strips and Glucometers	Test Strips	Type 1 and type 2 diabetes mellitus	300 test strips/30 days
	Glucometers		One meter/365 days

Test Strips

Initial Evaluation

FreeStyle, FreeStyle Lite, FreeStyle InsuLinx, FreeStyle Precision Neo, Precision Xtra, Contour, and Contour Next are the preferred diabetic test strips.

- There is no prior authorization required on these preferred agents, unless requesting over the allowed quantity limits noted above.

I. **Non-preferred test strips** may be considered medically necessary when the following criteria below are met:

A. Member is using one of the following quantity limits**:**

1. 300 test strips per 30-day supply; **OR**
2. Above 300 test strips per 30-day supply and there is documentation of medical necessity submitted for a quantity above 300 test strips per 30-day supply; **AND**

B. Use of ALL of the following preferred test strips have been ineffective:

1. FreeStyle
2. FreeStyle Lite
3. FreeStyle InsuLinx
4. FreeStyle Precision Neo
5. Precision Xtra
6. Contour
7. Contour Next; **OR**

C. Member uses test strips with a glucometer built into, or communicates with, an insulin pump and preferred products cannot be utilized; **OR**
D. Member uses a voice meter due to vision impairment

Glucometers

Initial Evaluation

FreeStyle Lite, FreeStyle Freedom Lite, Contour Next Gen, Contour Next EZ, and Contour Next One are covered at zero cost share to the member only through the manufacturer Free Meter Program. Members can access their free meter by using any of the options below:

- **By Pharmacy:**
  - Ascensia:
    - BIN: 018844
    - PCN: 3F
    - Group: MGDCARE
    - ID: CNMC7246982
  - Abbott:
    - BIN: 610020
    - PCN: PDMI
    - Group: 99992432
    - ID: ERXNAVITUS
- **By Telephone:**
  - Ascensia: 1-800-401-8440, use offer code BDC-MOD
  - Abbott: 1-866-224-8892, use offer code KYDCW4DQ
- **By Web:**
  - Ascensia:
    - Contour Next Gen Meter: www.ascensiadiabetes.com/meters-and-strips-savings/free-contour-next-gen-meter/
    - Contour Next EZ Meter: www.ascensiadiabetes.com/meters-and-strips-savings/free-contour-next-ez-meter/
    - Contour Next One Meter: www.ascensiadiabetes.com/meters-and-strips-savings/free-contour-next-one-meter/
  - Abbott: www.choosefreestyle.com , use offer code KYDCW4DQ

I. **All other meters** may be considered medically necessary when the following criteria below are met:
   A. Documentation that use with FreeStyle Lite, FreeStyle Freedom Lite, Contour Next Gen, Contour Next EZ, and Contour Next One is contraindicated; **OR**
   B. Member uses an insulin pump that cannot communicate with any of the following meters: FreeStyle Lite, FreeStyle Freedom Lite, Contour Next Gen, Contour Next EZ, and Contour Next One; **OR**
   C. Member requires the use of a voice meter due to vision impairment

Renewal

I. Same as initial criteria

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include new meter program information from Ascensia; Updated “Contour Next” name to “Contour Next Gen”;	01/2023
Rearranged questions to better capture intent and clarify path to coverage. Updated Glucometer table to more accurate billing information and website information	02/2022
Separated out non-preferred glucometers and test strips criteria. Added in box regarding billing preferred glucometers. Updated Renewal language to run through initial each time.	01/2021
Updated requirements language to be more consistent with plan’s standard language. Adjusted order of requirements to enhance clarity.	12/2020
Criteria transitioned into policy with medically not necessary and renewal evaluation sections added.	01/2020
Criteria created	01/2016

diazoxide choline (Vykat XR™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP328

Description

Diazoxide choline (Vykat XR ™) is an adenosine triphosphate (ATP)-dependent potassium channel agonist, that increases blood glucose, due to inhibition of insulin release from the pancreas.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
diazoxide choline (Vykat XR)	Treatment of hyperphagia in patients with Prader-Willi syndrome (PWS)	25mg XR Tablets	120 tablets/30 days
		75mg XR Tablets	210 tablets/30 days
		150 mg XR Tablets	120 tablets/30 days

Initial Evaluation

I. **Diazoxide choline (Vykat XR)** 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 an endocrinologist, geneticist, pediatrician, or neurologist; **AND**
   C. Member's weight is documented within the last 3 months; **AND**
   D. A diagnosis of **Prader-Willi syndrome** when the following are met:
      1. Diagnosis is confirmed by documentation of genetic analysis with identification of abnormal DNA methylation of chromosome 15q11.2-q13; **AND**
      2. Documentation the member has moderate to severe hyperphagia, defined as frequent (more than once per week) food-related aggression or manipulation and food preoccupation that interferes with normal daily activities; **AND**
      3. Documentation of caregiver having implemented and intends to continue strategies to establish a food-secure environment (e.g., locked food storage, behavior modifications, therapy, etc.)

II. Diazoxide choline (Vykat XR) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Prader Willi Syndrome *without* hyperphagia

III. Diazoxide choline (Vykat XR) is considered investigational when used for all other conditions, including but not limited to:
   A. Hyperinsulinemic hypoglycemia

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's weight has been documented in the last 3 months; **AND**
IV. Chart note documentation member has exhibited an improvement or decrease in hyperphagic and food-related behaviors [e.g., food related preoccupations, food-seeking behaviors]

Supporting Evidence

I. Diazoxide choline (Vykat XR) is a long-acting salt formulation of diazoxide (also known as DCCR), for the treatment of hyperphagia in adults and children four years of age and older with Prader-Willi syndrome (PWS). The proposed mechanism of action (MOA) for diazoxide is as a potassium channel opener; however, the exact MOA is unknown. Diazoxide suspension (brand name Proglycem) has been available for the treatment of hyperinsulinemic hypoglycemia in pediatric and adult patients when other specific medical therapy or surgical management for hypoglycemia is unsuccessful or is not feasible.
II. Prader-Willi syndrome (PWS) is characterized by early failure to thrive, hypotonia in infants (i.e. low muscle tone/floppy infant syndrome), followed by the onset of hyperphagia sometime in early childhood, leading to obesity. Hyperphagia, a persistent sensation of hunger, is a key manifestation of PWS. Some patients may experience periods without hyperphagia, and the severity of symptoms varies. Individuals with PWS have shown high rates of choking, accidents, and gastrointestinal perforation that is presumably related to uncontrolled hyperphagia, and a study found that food-seeking behavior contributed to about one-third of all reported deaths among patients with PWS and about one-half of deaths among patients with PWS under 18 years of age. European guidelines on Prader-Willi syndrome (2024) state that hyperphagia and food-seeking behaviors begin in early childhood and persist throughout the patient's life. Food security practices can include physical interventions, such as locks on refrigerators or cupboards.
III. Hyperphagia is managed by supervising meal preparation and food intake, implementing food security measures (e.g., locks on cabinets and refrigerators), and supervision of the person with PWS. These interventions may impact activities of daily living, and may prevent full participation in school, employment, social life, and independent living, all of which are burdensome and impact quality of life for patients, families, and caregivers.
IV. A diagnosis of PWS is completed through the presence of characteristic clinical features and confirmed by genetic testing. Prader-Willi syndrome arises due to absent paternal expression on chromosome 15q11.2-q13, which is verified via genetic testing. Due to the specialized skills required for evaluation and diagnosis of this condition as well as the monitoring required in conjunction with diazoxide choline (Vykat XR) treatment coverage requires treatment to be prescribed by or in consultation with a physician who specializes in PWS, such as an endocrinologist, geneticist, pediatrician, or neurologist.

V. Treatment of PWS consists of management of an individual patient's symptoms. In 2000, the FDA approved the use of human growth hormone (hGH) therapy to normalize growth and improve body composition in patients with PWS. Prior to the approval of diazoxide choline (Vykat XR), there were no treatment options for PWS that addressed hyperphagia. The current standard of care for the management of hyperphagia in PWS includes food restriction methods and behavioral interventions. Guidelines additionally mention dietary strategies and exercise programs to prevent weight gain. Diazoxide choline (Vykat XR) is the first treatment indicated for hyperphagia in adults and children four years of age and older with PWS. Guidelines have not been updated since the approval of diazoxide choline (Vykat XR). Additionally, there are no consensus guidelines on the use of anti-obesity medications (e.g., topiramate, metformin, liraglutide, semaglutide, tirzepatide, etc.) in PWS.

VI. The safety and efficacy of diazoxide choline (Vykat XR) were evaluated in two trials. The DESTINY-PWS (C601) trial was a 13-week, randomized double-blind, placebo-controlled study in 126 patients. The primary endpoint was the change in hyperphagia from baseline through week 13 measured using the Hyperphagia Questionnaire for Clinical Trials (HQ-CT), a 9-item, validated questionnaire that assessed food-related behaviors associated with hyperphagia. The HQ-CT total score ranges from 0 to 36 (higher scores indicate greater severity of hyperphagia and food-related behaviors). Treatment with diazoxide choline did not demonstrate a statistically significant reduction from baseline HQ-CT compared to placebo. Although diazoxide choline did not significantly improve the primary endpoint of hyperphagia overall, it did improve this endpoint in participants with severe hyperphagia.

VII. Upon completion of DESTINY-PWS, patients (N=115) entered Study C602-OLE, which was a long-term, open-label, maintenance trial. Patients who successfully completed this phase entered a 16-week double-blind placebo-controlled randomized withdrawal treatment phase (N=77). Patients that continued diazoxide choline treatment saw a 2.6-point increase in HQ-CT scores, while those on placebo saw a 7.6-point increase — a 5-point difference that was statistically significant. The manufacturer notes that at least 31% of patients (N=38) who had at least 1 post-baseline assessment of HQ-CT (N=124) experienced interrupted visits, possibly due to COVID-19 as a contributing factor to missing data in C601.

VIII. Although patients who switched from diazoxide choline to placebo demonstrated a statistically significant worsening in hyperphagia compared to those who remained on treatment, a significant clinical benefit (e.g., a reduction in food-seeking behaviors) of diazoxide choline (Vykat XR) has not been established. While the HQ-CT has been developed and validated for use in the assessment of hyperphagia related behaviors in clinical studies in PWS, the quality of the evidence is poor given one RCT trial (DESTINY-PWS) with higher degree of design/execution, but did not show statistically significant results and the OLE trial with lower (acceptable) degree of design/execution, but did result in statistically significant change in HQ-CT. Although this change was considered statistically significant, it did not meet the clinical significance of a 7-point change. There is a general positive trend seen when diazoxide is used long term for potentially addressing behavioral problems in PWS based on two RCTs. Additional applicability concerns include, the HC-QT questionnaire being subject to caregiver bias, potential Attrition Bias (more discontinuations in treatment arm compared with placebo arm, due to adverse events).

IX. The primary clinical outcome assessment for hyperphagia-associated behaviors in PWS is the HQ-CT, a caregiver-reported assessment of hyperphagic behaviors during the past 2 weeks including food seeking behaviors, tendency toward being upset or distressed when denied food or asked to stop talking about food and the extent to which these behaviors interfere with daily life, which has been shown to be sensitive to change in the setting of clinical trials for drugs targeting hyperphagia in the PWS population. However, this questionnaire has not been fully characterized in real-word setting in a large PWS population, nor in typically developing individuals. The HQ-CT consists of nine items with responses ranging from 0-4 (best to worst). Scores from 9 items are summed for a possible total score range of 0-36, where higher scores indicate more severe hyperphagia symptoms. A reduction in score from baseline indicates improvement in symptoms.

X. The most common adverse reactions reported in clinical trials (incidence ≥10% and at least 2% greater than placebo) were hypertrichosis, edema, hyperglycemia, and trash. Diazoxide choline (Vykat XR) has warnings for hyperglycemia and risk of fluid overload. Per the diazoxide choline (Vykat XR) prescribing information, it is recommended prior to initiating treatment to test fasting plasma glucose (FPG) and HbA1c and optimize blood glucose in patients who have hyperglycemia. Fasting glucose and HbA1c monitoring is also recommended during treatment and for dosage modifications based on results, as it is recommended to interrupt treatment or reduce dosage for clinically significant elevations in fasting glucose or HbA1c, as well as considerations for dosage reduction or interruption for clinically significant fluid overload.

XI. Requirements for coverage include ensuring the member has the ability to swallow, as the diazoxide choline (Vykat XR) tablets must be taken whole, and not split, crushed, or chewed, due to compromising the extended-release characteristics of treatment. Swallowing and behavioral concerns are common in the PWS population and confirming that the member can swallow tablets prior to approval is medically necessary to ensure the integrity of treatment and reduce drug waste.

Investigational or Not Medically Necessary Uses

I. Diazoxide choline (Vykat XR) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Prader Willi Syndrome without hyperphagia
      i. Diazoxide choline (Vykat XR) is only indicated for the treatment of hyperphagia in patients with Prader-Willi syndrome. No data is available on the treatment of hyperphagia in patients without documented Prader-Willi syndrome, and is therefore considered not medically necessary.
   B. Hyperinsulinemic hypoglycemia
      i. Diazoxide choline (Vykat XR) tablets are not FDA-approved for use in hyperinsulinemic hypoglycemia. Diazoxide suspension (generic and brand Proglycem) is FDA-approved for hyperinsulinemic hypoglycemia and available for use when other specific medical therapy or surgical management for hypoglycemia is unsuccessful or is not feasible. Per diazoxide choline (Vykat XR) prescribing information, these agents should not be substituted based on differences in their pharmacokinetic profiles.

Appendix

I. Diazoxide choline (Vykat XR) is administered orally once daily with the starting dosage and titration schedule based on body weight. The maximum recommended dosage is 5.8 mg/kg/day or 525 mg per day.

Weight (kg)	Starting Dosage	Titration Dosage	Titration Dosage	Target Maintenance Dosage
	Weeks 1 and 2	Weeks 3 and 4	Weeks 5 and 6	
20 to 30	25 mg	50 mg	75 mg	100 mg
30 to 40	75 mg	150 mg	150 mg	150 mg
40 to 65	75 mg	150 mg	225 mg	225 mg
65 to 100	150 mg	225 mg	300 mg	375 mg
100 to 135	150 mg	300 mg	375 mg	450 mg
> 135 kg	150 mg	300 mg	450 mg	525 mg

References

1. VYKAT XR. Package insert. Soleno Therapeutics Inc; April 2025.
2. Scheimann A. Prader-Willi syndrome: Clinical features and diagnosis. In: Geffner M, Heyman M, Kremen J, eds. UpToDate. UpToDate;2025. Accessed September 4, 2025. https://www.uptodate.com/contents/prader-willi-syndrome-clinical-features-and-diagnosis
3. Shaikh MG, Barrett TB, Bridges N, et al. Prader-Willi syndrome: guidance for children and transition into adulthood. Endocr Connect. 2024; 13(8):e240091
4. Butler MG, et al. Causes of death in Prader-Willi syndrome: Prader-Willi Syndrome Association (USA) 40-year mortality survey. *Genet Med.* 2017;19(6):635-642. doi:10.1038/gim.2016.178
5. Miller J, et al. Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: a double-blind, placebo-controlled trial. *J Clin Endocrinol Metab.* 2023;108(7):1676–1685. doi:10.1210/clinem/dgad014
6. Miller JL, Gevers E, Bridges N, et al. Diazoxide choline extended-release tablet in people with Prader-Willi syndrome: results from long-term open-label study. *Obesity (Silver Spring)*. 2024;32(2):252-261. doi:10.1002/oby.23928
7. Strong TV, et al. Behavioral changes in patients with Prader-Willi syndrome receiving diazoxide choline extended-release tablets compared to the PATH for PWS natural history study. *J Neurodev Disord.* 2024;16(1):22. doi:10.1186/s11689-024-09536-x
8. Matesevac L, et al. Analysis of Hyperphagia Questionnaire for Clinical Trials (HQ-CT) scores in typically developing individuals and those with Prader-Willi syndrome. *Sci Rep*. 2023;13(1):20573. doi:10.1038/s41598-023-48024-5
9. Matesevac, L., Vrana-Diaz, C.J., Bohonowych, J.E. *et al.* Analysis of Hyperphagia Questionnaire for Clinical Trials (HQ-CT) scores in typically developing individuals and those with Prader-Willi syndrome. *Sci Rep* 13, 20573 (2023). https://doi.org/10.1038/s41598-023-48024-5

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
Human Growth Hormone Policy	Short stature associated with Prader-Willi Syndrome
EOCCO: setmelanotide (Imcivree®) Policy	Chronic weight management in monogenic or syndromic obesity due to POMC, PCSK1, or LEPR deficiency, variants interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)
	Chronic weight management in monogenic or syndromic obesity due to Bardet-Biedl syndrome (BBS)*

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	10/2025

dichlorphenamide (Keveyis®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP121

Description

Dichlorphenamide (Keveyis) is a carbonic anhydrase inhibitor; however, the mechanism by which it exerts its therapeutic effects in periodic paralysis is unknown.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
dichlorphenamide (Keveyis)	Primary periodic paralysis	50 mg tablets	120 tablets/30 days
Generic dichlorphenamide			

Initial Evaluation

I. **Dichlorphenamide (Keveyis)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist or provider with experience in primary periodic paralysis (e.g., physiatrist); **AND**
   B. Member is 18 years of age or older; **AND**
   C. If request is for brand dichlorphenamide (Keveyis), treatment with generic dichlorphenamide has been ineffective, contraindicated, or not tolerated; **AND**
   D. A diagnosis of **primary hypokalemic or hyperkalemic periodic paralysis** when the following are met:
      1. Provider attestation that lifestyle modifications to reduce attack frequency and severity (e.g., dietary changes, exercise adjustments) have been maximized and have been ineffective or insufficient alone; **AND**
      2. Documentation of baseline attack frequency and average duration (required for renewal evaluation); **AND**
      3. Treatment with acetazolamide has been ineffective, or not tolerated; **AND**
         i. For hypokalemic periodic paralysis: treatment with a potassium-sparing diuretic (e.g., spironolactone, triamterene, eplerenone) in combination with acetazolamide has been ineffective, contraindicated, or not tolerated (Note: if acetazolamide is not tolerated, monotherapy with a potassium-sparing diuretic is required); **OR**
         ii. For hyperkalemic periodic paralysis: treatment with hydrochlorothiazide has been ineffective, contraindicated, or not tolerated.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ArrayRx administered by moda HEALTH

II. Dichlorphenamide (Keveyis) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Glaucoma

III. Dichlorphenamide (Keveyis) is considered investigational when used for all other conditions, including but not limited to:
   A. Periodic paralysis not characterized as hyperkalemic or hypokalemic
   B. Pediatric periodic paralysis

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 lifestyle modifications to reduce attack frequency and severity (e.g., dietary changes, exercise adjustments) continue to be practiced; **AND**
IV. Documentation showing reduction in attack frequency, duration, or severity compared to baseline; **AND**
V. If request is for brand dichlorphenamide (Keveyis), treatment with generic dichlorphenamide has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. Periodic paralysis (PP) is a rare neuromuscular disorder due to a defect in muscle ion channels, and is characterized by attacks of painless muscle paralysis and generalized weakness. The majority of PP cases are hereditary and not a result of hypo or hyperkalemia. Two types of PP include hypokalemic and hyperkalemic, pertaining to the serum level of potassium at the time of attack. Attacks may last minutes, hours, or days causing increased morbidity and impaired quality-of-life. Nonpharmacologic interventions may reduce frequency or severity of attacks. For hypokalemic PP, effective strategies may include a low sodium and low carbohydrate diet, supplementation with potassium, limiting vigorous exercise, minimizing stress, limiting alcohol intake, and avoidance of fasting. For hyperkalemic PP, effective strategies may include avoidance of potassium-rich foods, avoidance of fasting, minimizing exposure to cold, minimizing stress, and limiting vigorous exercise. When lifestyle modifications are ineffective or insufficient for preventing attacks, medication therapy may be considered (e.g., diuretics, thiazides, carbonic anhydrase inhibitors).
II. Given the difficulty with diagnosing PP and specialized management and treatment of the condition, prescribing by, or in consultation with, a specialist is required.
III. Dichlorphenamide (Keveyis) is indicated for the treatment of primary hypokalemic and hyperkalemic PP and related variants; however, it has only been evaluated in hypokalemic and hyperkalemic PP.

IV. Dichlorphenamide (Keveyis) has been evaluated in Phase 3 clinical trials of adults with hypokalemic and hyperkalemic PP patients. Overall, trials showed that therapy may help reduce 2-4 attacks per week compared to placebo; however, the studies has several limitations: patients transitioning from acetazolamide to dichlorphenamide did not have a washout period before entering the study, hypokalemic patients could supplement with potassium as required for acute attacks, and adverse effects (e.g., dysgeusia, cognitive issues, and paresthesia) were more common in the dichlorphenamide group – which may have led to unblinding the trial. Given these considerations, therapeutic effects may not be fully attributable to dichlorphenamide (Keveyis).

V. Other treatment strategies:
- Dichlorphenamide (Keveyis) may have an advantage in the level of trials available (Phase 3); however, given trial shortcomings listed above as well as the cost of treatment, trial of acetazolamide and one additional therapy (see below) are required. Empiric treatment with acetazolamide is standard of care, and is significantly less costly ($2-8 per day vs. $330-1300 per day). Acetazolamide and dichlorphenamide are in the same medication class and are expected to have similar tolerance. Contraindications to acetazolamide are the same as those to dichlorphenamide (Keveyis). Additionally, it has not been proven that dichlorphenamide (Keveyis) is superior to acetazolamide in safety or efficacy, as there are no comparative studies.
- For hypokalemic PP prophylaxis, potassium-sparing diuretics (e.g., spironolactone, triamterene, eplerenone) may be effective pharmacotherapy. These may be used in conjunction with carbonic anhydrase inhibitors or as monotherapy in patients that did not tolerate or experienced efficacy with carbonic anhydrase inhibitors. It has not been proven that dichlorphenamide (Keveyis) is superior to potassium-sparing diuretics in safety and efficacy as there are no comparative studies. Additionally, dichlorphenamide (Keveyis) is more costly; thus, trial of a potassium-sparing diuretic is required before coverage consideration of dichlorphenamide (Keveyis). Use in addition to, or as second-line treatment after, acetazolamide may maximize efficacy of these therapies and is required prior to coverage consideration of dichlorphenamide (Keveyis).
- For hyperkalemic PP, hydrochlorothiazide may be effective pharmacotherapy. It has not been proven that dichlorphenamide (Keveyis) is superior to hydrochlorothiazide in safety or efficacy as there are no comparative studies. Additionally, dichlorphenamide (Keveyis) is more costly; thus, trial of hydrochlorothiazide is required before coverage consideration of dichlorphenamide (Keveyis).

VI. Efficacy, if realized, should occur by two months of therapy. The prescribing information indicates that response should be evaluated after two months. Given variability of patient response, risk of therapy exacerbating the condition symptoms, and cost, documentation of improvement of attack frequency, severity or duration is required prior continuation of treatment. Of note, withdrawal from the study due to acute and severe worsening of symptoms occurred in two patients in clinical trials for dichlorphenamide (Keveyis). Without reduction in attack frequency, severity, or duration, therapy should not be continued. Three months is allowed for initial approval to allow time for assessment of response and continuity of care.

Investigational or Not Medically Necessary Uses

I. Dichlorphenamide (Keveyis) is not FDA-approved, or has not been sufficiently studied for safety and efficacy for the following conditions:
   A. Glaucoma: dichlorphenamide (Daranide) was FDA-approved for glaucoma in 1958, and it was subsequently thought to be effective, off-label, for periodic paralysis. Dichlorphenamide (Daranide) was discontinued in 2002, given lack of use for glaucoma and availability of many effective therapies for glaucoma. Therapy is now available from an alternative manufacturer, as brand Keveyis. Although dichlorphenamide has been utilized in glaucoma historically, at this time it is unproven if dichlorphenamide (Keveyis) is more likely to produce similar therapeutic results or is superior to other agents that could be utilized for glaucoma (i.e., ophthalmic carbonic anhydrase inhibitors). Additionally, it is not generally recognized as an appropriate treatment for this condition. Furthermore, dichlorphenamide (Keveyis) is significantly more costly that other therapies that could be utilized. Given these factors dichlorphenamide (Keveyis) is not medically necessary for treatment of gluacoma.
   B. PP not characterized as hypokalemic or hyperkalemic (i.e., Thyrotoxic PP, Andersen syndrome, etc.): dichlorphenamide (Keveyis) is indicated for the treatment of primary hyperkalemic PP, primary hypokalemic PP, and related variants; however, has only been evaluated in hypokalemic and hyperkalemic PP. Use for other variations of PP is considered experimental and investigational.
   C. Pediatric/adolescent PP: Dichlorphenamide (Keveyis) has not been sufficiently evaluated and is not FDA-approved in pediatric or adolescent patients. To date, one study has attempted to evaluate safety and efficacy of dichlorphenamide (Keveyis) in adolescent patients. The study included six adolescents that were exposed to therapy, five of which were evaluable for efficacy. Although median decrease from baseline in weekly attack frequency was numerically greater compared to placebo, the trial had multiple shortcomings. It was not powered to statistically evaluate changes in attack frequency for the adolescent subgroup, the trial duration was only nine weeks long, few patients were evaluated, and the dose varied between patients. Safety concerns included skin rash, dizziness, numbness, lightheadedness, slow thinking, nausea, weakness, and weight loss among adolescent patients. This trial did not sufficiently determine consequences of therapy in adolescents, and safety and efficacy in this population remains unknown; thus, is considered experimental and investigational. Lifestyle modifications and alternative therapies may be considered.

References

1. Keveyis [Prescribing Information]. Hawthorne, NY: Taro Pharmaceuticals; November 2019.
2. Statland JM, Fontaine B, Hanna MG, et al. Review of the Diagnosis and Treatment of Periodic Paralysis. Muscle Nerve. 2018;57(4):522-530.
3. Ciafaloni E, Cohen F, Griggs R. Efficacy and safety of dichlorphenamide for primary periodic paralysis in adolescents compared with adults. *Pediatr Neurol*. 2019;101:43-46.
4. Sansone VA, Burge J, McDermott MP, et al. Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. Neurology. 2016;86(15):1408-1416.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic dichlorphenamide to QL table; added requirement to t/f generic dichlorphenamide prior to us of branded Keveyis	01/2023
Criteria updated: Changed initial approval from two to three months, addition of age requirement, addition of requirement regarding lifestyle modifications, distinction between hyperkalemic and hypokalemic PP with additional associated medication trial. Updated renewal criteria to standard format and to allow only in the event of improvement in the condition. Update to latest policy format, addition of NMN and E/I indications.	07/2022
Prior authorization criteria transitioned to policy format. Updated initial and renewal durations as response should be seen within two months of therapy. Addition of specialist requirements. Addition of renewal criteria.	12/2019
Policy created	09/2015

dupilumab (Dupixent®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP019

Description

Dupilumab (Dupixent) is a subcutaneously administered monoclonal antibody (IgG4 Kappa) that antagonizes interleukin-4 (IL-4) and interleukin-13 (IL-13).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit†
dupilumab (Dupixent)	Asthma (moderate to severe)	200 mg/1.14mL pen injector or prefilled syringe	**Adult:** **First Month**: 4 (200mg OR 300mg) syringes/pens (4.56mL OR 8ml)/42 days **Maintenance:** 2 (200mg OR 300mg) syringes/pens (2.28mL OR 4ml)/28 days
			Pediatric (6-11 years of age)*: **No Loading Dose** **Maintenance:** • **15 to less than 30 kg:** 1 (200mg/1.14mL) syringes (2.28mL)/28 days; **OR** 1 (300mg/2mL) syringes/pens (2mL)/28days • **30 kg or more:** 2 (200mg/1.14mL) syringes/pens (2.28mL)/28 days
	Atopic Dermatitis (moderate to severe); Atopic Dermatitis (moderate to severe) and comorbid Asthma (Moderate to severe)	300 mg/2mL pen injector or prefilled syringe	**Adult:** **First Month:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** 2 (300mg) syringes/pens (4 mL)/28 days
			Pediatric (6 – 17 years of age): **First Month:** • **15 to less than 30 kg:** 2 (300mg) syringes/pens (4 mL)/28 days • **30 to less than 60 kg:** 4 (200mg) syringes/pens (4.56 mL)/28 days • **60 kg or more:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** • **15 to less than 30 kg:** 1 (300mg) syringes/pens (2 mL)/28 days • **30 to less than 60 kg:** 2 (200mg) syringes/pens (2.28 mL)/28 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

			• **60 kg or more:** 2 (300mg) syringes/pens (4 mL)/28 days
			Pediatric (6 months – 5 years of age): **No Loading Dose** **Maintenance:** • **5 to less than 15kg:** 2 (200mg) syringe/pen (2.28mL)/56 days • **15 to less than 30kg:** 2 (300mg) syringes/pens (4mL)/56 days
	Chronic rhinosinusitis with nasal polyposis	300 mg/2mL pen injector or prefilled syringe	2 (300mg) syringes/pens (4 mL)/28 days
	Prurigo Nodularis	300 mg/2mL pen injector or prefilled syringe	**First month:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** 2 (300mg) syringes/pens (4 mL)/28 days
	Eosinophilic esophagitis	200 mg/1.14mL pen injector or prefilled syringe 300 mg/2mL pen injector or prefilled syringe	• **15 to less than 30kg:** 2 (200mg) syringes/pens (2.28 mL)/28 days • **30 to less than 40kg:** 2 (300mg) syringes/pens (4 mL)/28 days • **40kg and more**: 4 (300mg) syringes/pens (8mL)/28 days
	Chronic obstructive pulmonary disease (moderate to severe)	300 mg/2mL pen injector or prefilled syringe	2 (300mg) syringes/pens (4 mL)/28 days
	Chronic Spontaneous Urticaria (CSU)	200 mg/1.14mL pen injector or prefilled syringe 300 mg/2mL pen injector or prefilled syringe	**Adult:** **First Month:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** 2 (300mg) syringes/pens (4 mL)/28 days
			Pediatric (12 to 17 years of age): **First Month:** • **30 kg to less than 60 kg:** 4 (200 mg) syringes/pens (4.56mL)/28 days • **60 kg or more:** 4 (300 mg) syringes/pens (8mL)/28 **Maintenance:**

			• **30 kg to less than 60 kg:** 2 (200 mg) syringes/pens (2.28mL)/28 days • **60 kg or more:** 2 (300mg) syringes/pens (4mL)/28 days
	Bullous Pemphigoid (BP)	300 mg/2mL pen injector or prefilled syringe	**First Month:** 2 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** 1 (300mg) syringe/pen (4 mL)/28 days

**For pediatric patients 6 to 11 years of age with asthma and co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage as per atopic dermatitis, which includes an initial loading dose*
†Dosage for patients with oral corticosteroid-dependent asthma or with comorbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyps may get an initial loading dose of 600 mg (two 300 mg injections) and subsequent maintenance dosage 300 mg every 2 weeks

Initial Evaluation

I. **Dupilumab (Dupixent)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, gastroenterology, immunology, or ENT (ear, nose, throat); **AND**
   B. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, mepolizumab, omalizumab, reslizumab, ensifentrine, etc.); **AND**
   C. A diagnosis of one of the following:
      1. **Atopic dermatitis (moderate to severe); AND**
         i. Member is six months of age or older; **AND**
            a. Body surface area (BSA) involvement of at least 10%; **OR**
               i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
         ii. Treatment with at least two of the following groups has been ineffective or not tolerated, unless ALL are contraindicated:
            a. Group 1: Topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
            b. Group 2: Topical calcineurin inhibitors (e.g. pimecrolimus cream, tacrolimus ointment)
            c. Group 3: Topical PDE-4 inhibitors (e.g. crisaborole [Eucrisa]); **OR**
      2. **Asthma (moderate to severe)**; **AND**
         i. Member is 6 years of age or older; **AND**
         ii. Member has **MODERATE** asthma as defined by one of the following:
            a. Daily symptoms
            b. Nighttime awakenings > 1x/week but not nightly
            c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs daily
            d. Some limitation to normal activities
            e. Lung function (percent predicted FEV1) >60%, but <80%

f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to mild asthma; **OR**

iii. Member has **SEVERE** asthma as defined by <u>one</u> of the following:
   a. Symptoms throughout the day
   b. Nighttime awakenings, often 7x/week
   c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs several times per day
   d. Extremely limited normal activities
   e. Lung function (percent predicted FEV1) <60%
   f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**

iv. Member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥150 cells/µL within the last 12 months; **AND**
   a. 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); **OR**

v. Member is dependent on oral corticosteroids for asthma control; **AND**

vi. Member is currently being treated with:
   a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
      i. 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}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
   b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**

vii. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**

3. **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**
   i. Member is 12 years of age or older; **AND**
   ii. Provider attests that the member has ALL of the following:
      a. Diagnosis of bilateral sinonasal polyposis as evidenced by an endoscopy or computed tomography (CT); **AND**
      b. Member has impaired Health-Related Quality of Life due to ongoing nasal congestion, blockage, or obstruction with moderate to severe symptom severity; **AND**
      c. Member has at least <u>one</u> of the following symptoms:
         i. Nasal discharge
         ii. Facial pain or pressure
         iii. Reduction or loss of smell; **AND**

iii. Member has current persistent symptomatic nasal polyps despite maximal treatment with an intranasal corticosteroid, unless ineffective, not tolerated, or contraindicated; **AND**

iv. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**

4. **Eosinophilic Esophagitis (EoE); AND**
   i. Member is one year of age or older; **AND**
   ii. Member weighs at least 15kg (33 lbs); **AND**
   iii. Provider attests that the member has ALL of the following:
      a. Symptoms consistent with eosinophilic esophagitis (e.g., dysphagia, food impaction, vomiting, central chest and upper abdominal pain, etc.); **AND**
      b. Eosinophil-predominant inflammation, consisting of a peak value of ≥15 eos/hpf or ~60 eosinophils/mm^2, as confirmed by endoscopic biopsy; **AND**
      c. Underlying cause of the member's condition is NOT considered to be any other allergic condition(s) or other form(s) of esophageal eosinophilia; **AND**
   iv. Member has experienced persistent EoE symptoms during or following an adequate trial of dietary restriction (e.g., empiric elimination diet); **AND**
   v. Treatment with at least one agent in each of the following classes has been ineffective, contraindicated, or not tolerated:
      a. Proton pump inhibitors (PPIs) for at least eight weeks; **AND**
      b. Swallowed topical corticosteroids (e.g., fluticasone, budesonide); **OR**

5. **Prurigo nodularis (moderate to severe); AND**
   i. Member is 18 years of age or older; **AND**
   ii. Member has a confirmed diagnosis of moderate to severe prurigo nodularis based on all of the following:
      a. Presence of nodules for at least 3 months; **AND**
      b. Disease is moderate to severe in severity (e.g., Worst-Itch Numeric Rating Scale (WI-NRS) score of at least 7, Investigator Global Assessment (IGA) score of 3 or 4; presence of at least 20 lesions on the body); **AND**
      c. Provider attests underlying cause of prurigo nodularis is not considered to be drug-induced or caused by other medical conditions, such as dermatillomania; **AND**
   iii. Treatment with at least one medium to very high potency topical corticosteroid has been ineffective, not tolerated, or contraindicated; **AND**
   i. Treatment with at least one of the following has been ineffective or not tolerated, unless ALL are contraindicated:

a. Topical calcineurin inhibitors (e.g. pimecrolimus cream, tacrolimus ointment)
b. Topical vitamin D analogue (e.g., calcipotriene)
c. Phototherapy (UVA or PUVB)
d. Systemic immunosuppressants (e.g. methotrexate or cyclosporine); **OR**

6. **Chronic obstructive pulmonary disease (COPD); AND**
   i. Member is 18 years of age or older; **AND**
   ii. Member has a confirmed diagnosis of moderate to severe COPD with an eosinophilic phenotype defined by all of the following:
      a. Post-bronchodilator FEV1/FVC ratio of <0.7; **AND**
      b. Post-bronchodilator FEV1 % predicted ≥30% and <80%; **AND**
      c. Documentation of blood eosinophils ≥300 cells/µL within the last 12 months; **AND**
   iii. Member is in COPD treatment Group E defined by one of the following:
      a. ≥2 moderate (e.g., treated with short-acting bronchodilators and oral corticosteroids ± antibiotics); **OR**
      b. ≥1 severe (e.g., required hospitalization or emergency room visit) exacerbation(s) within the last 12 months; AND
   iv. Member is currently being treated with:
      a. A triple therapy inhaler regimen comprising of a long-acting beta-2 agonist [LABA], a long-acting muscarinic antagonist [LAMA], and an inhaled corticosteroid (ICS), unless ICS is contraindicated, such as:
         i. LABA/LAMA/ICS combination product (e.g., Trelegy Ellipta, Breztri Aerosphere); **OR**
         ii. LABA/LAMA combination product (e.g., Anoro Ellipta, Stiolto Respimat, Bevespi Aerosphere); **AND**
            1. ICS has been contraindicated or not tolerated (e.g., beclomethasone (Qvar), budesonide (Pulmicort), ciclesonide (Alvesco), fluticasone (Arnuity, Flovent), mometasone (Asmanex)); **AND**
   v. Background controller medications (e.g., Trelegy, Anoro, Stiolto, Bevespi) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**

7. **Chronic Spontaneous Urticaria (CSU); AND**
   i. Member is 12 years of age or older; **AND**
   ii. Underlying cause of the member's condition is <u>NOT</u> considered to be any other allergic condition(s) or other form(s) of urticaria; **AND**
   iii. Member is avoiding triggers (e.g., NSAIDs, etc.); **AND**
   iv. Member had an inadequate response to a minimum (1) month trial on previous therapy of a second-generation H1-antihistamine product*; **AND**
   v. Member had an inadequate response to a minimum (1) month trial on previous therapy of at least **<u>one</u>** of the following:
      a. Updosing/dose advancement (up to 4-fold) of a second generation H1-antihistamine*

b. Add-on therapy with a leukotriene antagonist (e.g., montelukast, zafirlukast, etc.)
c. Add-on therapy with another H1-antihistamine*
d. Add-on therapy with a H2-antagonist (e.g. ranitidine, etc.)
e. Add-on therapy with cyclosporine; **OR**

8. **Bullous Pemphigoid (BP); AND**
   i. Member is 18 years or older; **AND**
   ii. Member has a confirmed diagnosis of **bullous pemphigoid** based on one of the following:
      a. Biopsy
      b. Blood test (e.g. enzyme-linked immunosorbent assay)
      c. Immunofluorescence; **AND**
   iii. The member has not received prior treatment with IL-4 or IL-13 antagonist (e.g. tralokinumab [Adbry], lebrikizumab [Ebglyss], etc.); **AND**
   iv. Treatment with at least two of the following groups has been ineffective or not tolerated, unless ALL are contraindicated:
      a. Group 1: topical corticosteroids (e.g., clobetasol, betamethasone, halobetasol, etc.)
      b. Group 2: oral corticosteroids (e.g., prednisolone, prednisone, etc.)
      c. Group 3: corticosteroid-sparing agents (e.g., doxycycline, dapsone, azathioprine, mycophenolate, methotrexate, etc.); **AND**
   v. Treatment will be used in combination with a tapering course of oral corticosteroids unless not tolerated or contraindicated

II. Dupilumab (Dupixent) is considered investigational when used for all other conditions, including but not limited to:
   A. Food and environmental allergies
   B. Other forms of esophagitis
   C. Gastrointestinal reflux disorder (GERD)
   D. Non-EoE eosinophilic gastrointestinal disorders
   E. Chronic spontaneous urticaria (CSU)
   F. Mucous membrane pemphigoid/prurigo and related conditions (e.g., pemphigoid nodularis, actinic purigo, lichen planus, multiple keratoacanthomas, epidermolysis bullosa pruriginosa, etc.)
   G. Emergency treatment of allergic reactions, including anaphylaxis
   H. Add on therapy for COPD when used in pediatric patients less than 18 years of age

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., benralizumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**

IV. A diagnosis of one of the following:

- **Atopic dermatitis (moderate to severe); AND**
  i. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms); **OR**
- **Asthma (moderate to severe); AND**
  i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
  ii. Background controller medications (e.g., ICS/LABA product listed above) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**
- **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**
  i. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps); **AND**
  ii. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**
- **Eosinophilic esophagitis; AND**
  i. Member has exhibited improvement or stability of disease (e.g., improvement in dysphagia/vomiting/abdominal pain, reduction in eosinophils); **OR**
- **Prurigo nodularis; AND**
  i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced itching/pruritis, improved skin appearance, reduction in number of nodules, etc.); **OR**
- **Chronic obstructive pulmonary disease; AND**
  i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced COPD exacerbations, reduced hospitalizations, improved FEV1); **AND**
  ii. Background controller medications (e.g., LAMA/LABA/ICS products (e.g., Trelegy Ellipta, Breztri Aerosphere) or LABA/LAMA products (e.g., Anoro Ellipta, Stiolto Respimat, Bevespi Aerosphere) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**
- **Chronic spontaneous urticaria (CSU)**; **AND**
  i. Member has exhibited improvement or stability of disease symptoms from baseline (e.g. decreased itch severity, decreased number of hives or decreased size of hives, etc.)
- **Bullous pemphigoid (BP); AND**
  ii. Member has exhibited improvement or stability of disease symptoms from baseline (e.g. decreased itch severity, decreased number of

blisters, etc.)

Supporting Evidence

I. Dupilumab (Dupixent) is FDA approved in the following settings:
- Moderate to severe asthma with eosinophilic phenotype in members 6 years of age or older
- Oral corticosteroid dependent asthma in members 6 years of age or older
- Moderate to severe atopic dermatitis for patients 6 months and older whose disease is not adequately controlled with topical prescription therapies
- Add-on maintenance treatment for patients 12 years of age or older with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)
- Treatment of adult patients with prurigo nodularis (PN)
- Add-on maintenance treatment for adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) associated with a history of exacerbations and eosinophilic phenotype.
- Treatment of adult and pediatric patients aged 12 years and older with chronic spontaneous urticaria (CSU) who remain symptomatic despite H1 antihistamine treatment

II. Dupilumab trials excluded concomitant biologic therapy; moreover, there is lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.

III. **Moderate to severe atopic dermatitis**
- For patients aged 12 years or older, dupilumab (Dupixent) was studied in four randomized, double-blind, placebo-controlled trials. In all four trials, investigators enrolled patients who had previous inadequate responses to a topical medication with a PGA score of at least three (scale of zero to four) and a minimum BSA involvement of ≥10%. In all four trials, patients in the dupilumab (Dupixent) arm achieved statistically significant improvement when compared to the placebo arm. See table below for details.

	Trial 1		Trial 2		Trial 3		Trial 4	
	DUPIXENT 300 mg Q2W N=224	PBO N=224	DUPIXENT 300 mg Q2W N=233	PBO N=236	DUPIXENT 300 mg Q2W + TCS N=106	PBO + TCS N=315	DUPIXENT 200 mg (<60 kg) or 300 mg (>60 kg) Q2W N=82	PBO N=85
% of patients with IGA 0 or 1	38%	10%	36%	9%	39%	12%	24%	2%
% of patients with EASI-75	51%	15%	44%	12%	69%	23%	42%	8%

- For patients aged 6 to 11 years, dupilumab (Dupixent) approval was based on the results from a 16-week, phase III, double-blind, placebo-controlled trial. Investigators enrolled pediatric patients who have had a previous inadequate response to a topical medication with a PGA score of four (scale of zero to four) and a minimum BSA involvement of ≥15%. Patients in both dupilumab arms achieved statistically significant improvements when compared to the placebo arm, see table below for details.

	<30 kg			≥30 kg		
	PBO + TCS n=61	Q4W + TCS n=61	Q2W + TCS n=63	PBO + TCS n=62	Q4W + TCS n=61	Q2W + TCS n=59

% of patients with IGA 0 or 1	13.1%	29.5% p<0.05	20.6%	9.7%	36.1% p<0.001	39% p<0.001
% of patients with EASI-75	27.9%	75.4% p<0.0001	60.3% p<0.001	25.8%	63.9% p<0.0001	74.6% p<0.0001

- For patients aged 6 months to 5 years, dupilumab (Dupixent) approval was based on the safety results from a 16-week trial consisting of 161 patients with a diagnosis of moderate-to-severe atopic dermatitis who were using dupilumab (Dupixent) in combination with a topical corticosteroid (AD-1539). Additionally, long-term safety of dupilumab (Dupixent) with or without a concomitant topical corticosteroid was evaluated in a 52-week open-label extension study consisting of 180 pediatric patients with atopic dermatitis (AD-1434); the majority of patients received dupilumab (Dupixent) dosed at 300mg every 4 weeks. The safety profile of dupilumab (Dupixent) with or without concurrent topical corticosteroid was similar between these two studies and consistent with the known safety profile of this medication in the adult and pediatric 6–17-years-old population. Notably, hand-foot-and-mouth disease and skin papilloma were reported in 9 (5%) and 4 (2%) of subjects, respectively. However, none of these cases led to study drug discontinuation during the trial.
- Treatments for mild-to-moderate atopic dermatitis include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and/or crisaborole (Eucrisa) – a PDE4 inhibitor, and phototherapy. 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.
- 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.
- 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, include 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 a high disease burden (BSA ≥ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.

IV. **Moderate to severe asthma**

- Dupilumab (Dupixent) was studied in three randomized, double-blind, placebo-controlled, multicenter trials. These trials did not require a minimum baseline blood eosinophilic count; mean baseline blood eosinophilic count for all trials were 353 cells/mcL. Trials 2 and 3 excluded patients with a screening blood eosinophil level of >1500 cells/mcL. Trials 1 and 2 required patients to have a history of at least one asthma exacerbation that required systemic corticosteroid treatment, or an emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry; patients continued background asthma treatment throughout the study. Trial 3 required dependence on daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus an additional controller(s).
    i. Trial 1: Patients enrolled were at least 18 years of age with moderate to severe asthma on a medium or high-dose ICS and a LABA. Patients were randomized to receive either dupilumab (Dupixent) 200 mg or 300 mg every other week (Q2W) or every 4 weeks following an initial dose of 400 mg, 600 mg, or placebo. The primary endpoint was mean change from baseline to Week 12 in FEV1 in patients with baseline blood eosinophil ≥300 cells/mcL receiving 200 mg, 300mg, or placebo, which were 25.9%, 25.8%, and 10.2%, respectively. Mean difference compared to placebo for the 200 mg and 300 mg were 0.26 (95% CI 0.11, 0.4) and 0.21 (95% CI 0.06, 0.36), respectively.
    ii. Trial 2: Patients enrolled were at least 12 years of age with moderate to severe asthma on a medium to high-dose ICS and a minimum of one and up to two additional controller medications. Patients were randomized to receive either dupilumab (Dupixent) 200 mg or 300 mg every 2 weeks following initial dose of 400 mg, 600 mg, or placebo. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo-controlled period receiving 200 mg vs placebo or 300 mg vs placebo, which were RR 0.52 (95% CI 0.41, 0.66) and RR 0.54 (95% CI 0.43, 0.68), respectively, and change from baseline in FEV1 at Week 12 receiving 200 mg vs placebo or 300mg vs placebo, which were 29% vs 15.9% and 32.5% vs 14.4%. Mean difference compared to placebo for the 200 mg and 300 mg were 0.21 (95% CI 0.13, 0.29) and 0.24 (95% CI 0.16, 0.32), respectively.
    iii. Trial 3: Patients enrolled were at least 12 years of age with asthma who required daily OCS in addition to regular use of high-dose ICS plus an additional controller. Patients were randomized to receive either dupilumab (Dupixent) 300 mg or placebo every 2 weeks for 24 weeks following an initial dose of 600 mg or placebo. Patients continued existing asthma therapy during the trial; OCS dose was reduced every 4 weeks during the OCS reduction phase (Weeks 4 to 20) as long as asthma control was maintained. The primary endpoint was the percent of reduction from baseline of the final oral corticosteroid dose at week 24 while maintaining asthma control in those receiving either 300 mg or placebo, which was 90% (95% CI 60%, 80%) vs 42% (95% CI 33%, 51%), respectively.
- The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biologics, after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4

include high dose ICS-LABA or add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5, or add-on low dose OCS, though guidelines note to consider side effects.

V. **Chronic rhinosinusitis with nasal polyposis (CRSwNP)**

- Dupilumab (Dupixent) approval was based on the results from two phase 3 pivotal trials SINUS-24 and SINUS-52. SINUS-24 was a 24-week study, while SINUS-52 was a 52-week study. Both trials evaluated dupilumab (Dupixent) 300mg administered every two weeks combined with standard-of-care mometasone furoate nasal spray (MFNS) and compared to placebo injection plus MFNS. In both trials, there were two co-primary endpoints, improvement in nasal congestion/obstruction severity and reduction in nasal polyps. At 24 weeks, patients in the dupilumab (Dupixent) arm achieved statistically significant improvements when compared to the placebo arm.
    i. Fifty-seven percent and 51% improvement in their nasal congestion/obstruction severity compared to a 19% and 15% improvement with placebo in SINUS-24 and SINUS-52, respectively.
    ii. Thirty-three percent and 27% reduction in their nasal polyps score compared to a 7% and 4% increase with placebo in SINUS-24 and SINUS-52, respectively.
- Dupilumab (Dupixent) is approved as an add-on maintenance treatment for patients aged 12 years of age or older with inadequately controlled CRSwNP. Use of dupilumab (Dupixent) is supported by data from the SINUS-24 and SINUS-52 trials in adults with CRSwNP, that showed dupilumab significantly improved nasal congestion/obstruction severity, nasal polyp size and sense of smell compared with placebo at 24 weeks, while also reducing the need for systemic corticosteroids and surgery. The expanded approval was also supported by current pharmacokinetic and safety data for adolescents using the drug for other approved indications.
- Guidelines and compendia recommend the use of topical saline irrigation and intranasal corticosteroids (INCS) as initial treatment options in CRSwNP. Intranasal corticosteroids (INCS) have a positive impact on the disease and improve symptoms, reduce nasal polyp size, reduce nasal poly recurrence, and improve sense of smell. The guidelines also recommend short-term treatment with oral steroids in patients with CRSwNP to reduce symptoms and decrease nasal poly size. Biologics are considered in patients where their disease remains uncontrolled despite appropriate medical treatment and endoscopic sinus surgery (ESS).
- There are no completed head-to-head studies comparing biologic agents for treatment of CRSwNP. However, dupilumab (Dupixent) has been consistently found to be the most effective in multiple systematic reviews and indirect comparisons. A head-to-head comparison of omalizumab (Xolair) versus dupilumab (Dupixent) for treatment of CRSwNP is underway (NCT04998604) with an estimated completion in early 2025.

VI. **Eosinophilic esophagitis (EoE)**

- Dupilumab (Dupixent) was approved for the treatment of eosinophilic esophagitis (EoE) in patients aged 12 years and older weighing at least 40kg based on data from a single Phase 3, randomized, double-blind, placebo-controlled (Liberty EoE TREET) trial consisting of three parts (A, B, and C).
- Results from Parts A and B 24-week treatment periods of the Liberty EoE TREET trial were evaluated for the FDA approval of the EoE indication, as Part C is still ongoing. In both parts, there were two co-primary endpoints: the proportion of subjects

achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24 and the absolute change in the subject reported DSQ score from baseline to Week 24. Dupilumab (Dupixent) met the co-primary endpoint in both Parts A and B for the 300mg weekly dose only. The dupilumab (Dupixent) 300mg every two-week dosing failed to meet statistical significance for the absolute change in subject reported DSQ score. Notably, the FDA has chosen to only approve the 300mg weekly dose for treatment of EoE.

	Part A		Part B		
	Dupixent 300mg QW N = 42	**Placebo N = 39**	**Dupixent 300mg QW N = 80**	**Dupixent 300mg Q2W N = 81**	**Placebo N = 79**
Co-primary Endpoints					
Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)	25* (59.5)	2 (5.1)	47* (58.5)	49* (60.5)	5 (6.3)
Absolute change from baseline in DSQ score, LS mean (SE)	-21.9* (2.5)	-9.6 (2.8)	-23.8* (1.9)	-14.4 (1.86)	-13.9 (1.9)
*denotes statistically significant difference compared to placebo					

- No new safety concerns emerged during the Liberty EoE TREET trials. Overall, approximately 85% of patients treated with dupilumab (Dupixent) during the clinical trial experienced an adverse event, although most of the treatment emergent adverse events were considered to be mild or moderate. The most common adverse events experienced by patients included injection-site reaction, including erythema, pain and swelling, headache and diarrhea.
- EoE is a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Diagnosis of EoE is made when all of the following are present: symptoms related to esophageal dysfunction (e.g., dysphagia, food impaction, abdominal pain), eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥15 eosinophils per high power field (HPF) (or 60 eosinophils per mm2), and exclusion of other conditions that may be responsible for or contributing to symptoms of esophageal eosinophilia (e.g., eosinophilic gastritis, GERD, hyper-eosinophilic syndrome, Crohn's disease, etc.). Because EoE has a strong association with allergies, patients are recommended to undergo an evaluation by an allergist to rule out allergy-related conditions. Additionally, due to overlap of symptoms with GERD and alimentary tract involvement, evaluation by a gastroenterologist may also be appropriate.
- Dietary restriction is used as a first-line strategy to combat EoE symptoms, including dysphagia and abdominal pain. The most commonly used dietary therapy is an empiric elimination diet based on the concept of avoiding the six foods/food groups that most commonly cause the majority of IgE-mediated food reactions (e..g, milk, egg, soy, wheat, peanuts/tree nuts, fish/shellfish). Other dietary therapies include testing-directed elimination diets, which utilize antigen or allergy testing to eliminate foods that trigger a positive test result, and an elemental diet, which utilizes amino acid based (elemental) formula. However, these other methods are less commonly used to due to expense and difficulty to follow.
- Dupilumab (Dupixent) is the first medication to gain FDA approval for the EoE indication, and there are limited pharmacological treatment options used off-label

for this indication. AGA guidelines strongly recommend treatment with swallowed topical steroids. Supported therapies in this class include fluticasone and budesonide. Fluticasone is administered as a metered-dose inhaler that is sprayed into the mouth and swallowed, while budesonide is administered as a slurry (nebulizer ampules mixed with sucralose) over the course of five to ten minutes. Guidelines also conditionally recommend the use of proton pump inhibitors (PPIs); however, PPIs have been considered standard of care for EoE and subjects in the LIBERTY EoE TREET trial were required to have failed an 8-week treatment with a high-dose PPI (i.e., twice daily dosing) prior to inclusion in the study population. Therefore, although there is limited guideline support for use of PPIs in EoE, requiring prior treatment with PPIs is appropriate as efficacy and safety of dupilumab (Dupixent) in patients with EoE and no prior use of PPIs remains unknown.

VII. **Prurigo nodularis (PN)**

- Prurigo nodularis (PN) is distinct from other pruritic disorders as its core symptoms include presence of multiple firm, nodular lesions distributed symmetrically on the trunk, arms, and/or legs with chronic pruritis lasting greater than 6 weeks in duration. A history of a persistent scratch-itch cycle is accompanied by burning, stinging, pain, and scarring, significantly impacting quality of life. Complete resolution of lesions may not occur even if there is remission in pruritic symptoms.
- Literature suggests up to 60% of patients with PN have a history of atopic conditions (atopic dermatitis, allergic rhinitis, asthma, etc.), but drug induced PN (e.g., opioids, ACE inhibitors, etc.) or PN due to other medical conditions such as neuropathy or psychiatric disease (i.e. dermatillomania, obsessive compulsive disorder, etc.) should be considered and ruled out.
- Treatment approaches: Dupilumab (Dupixent) is the first FDA-approved treatment for adults with PN. Efficacy for PN therapies are based on case reports or small observation studies, and all treatments are currently used off-label. Clinical experience and expert consensus guidelines recommend the use of the following treatment modalities with goals to reduce pruritis and reduce/heal PN nodules, often used in combination:
    i. Similar to atopic dermatitis management, moderate to very high potency topical corticosteroids (TCS) are often used as first line therapy based on clinical experience and expert consensus guideline recommendations for PN. Treatment with intralesional corticosteroids injection(s) (e.g., triamcinolone 5 – 20mg/mL) may also be an option for thick PN nodules to reduce pruritis and flatten large PN lesions. Trials of calcineurin inhibitors, capsaicin, may be used in recalcitrant disease or when TCS are not appropriate, although their use is based on small observational studies. The efficacy of topical therapies for PN has not been adequately evaluated in randomized trials.
    ii. Narrowband ultraviolet B (UVB) phototherapy is occasionally used as an adjunct therapy for patients who have not responded to topical pharmacotherapy, based on evidence from small observational studies and one randomized study. In one study, ten patients treated with UVB therapy 2-3 times weekly in combination with TSC reported significant improvement in skin lesions after 16 weekly treatments; however, accessing therapy may prove to be a barrier for many patients.

iii. Systemic therapies: oral immunosuppressants, such as low dose methotrexate and cyclosporine, have been used off-label with success in reducing the number and severity of skin lesions. Although safety and efficacy of oral systemic therapies for PN have not been evaluated in randomized trials, expert consensus guidelines conditionally recommend systemic immunologic treatments as reasonable therapy options. Use of systemic therapies with antipruritic activity, including, but not limited to gabapentin, pregabalin, amitriptyline, thalidomide, or naltrexone, have been used in clinical practice; however, data in PN is limited and efficacy cannot be determined.

- Prurigo nodularis rarely occurs in pediatric patients and the safety and efficacy of dupilumab (Dupixent) for the treatment of PN in patients younger than 18 years of age has not been established.
- The duration of initial approval at six months is derived from the evidence reported in the dupilumab (Dupixent) trials for PN, whose results were reported at 12 and 24 weeks.
- Safety and efficacy of dupilumab (Dupixent) for adults with PN was evaluated in two Phase III, randomized, double blind, placebo-controlled trials (LIBERTY-PN-PRIME and PRIME2). The trials evaluated a total of 311 participants ages 18 to 80 years of age with a clinical diagnosis of uncontrolled PN for at least 3 months in duration, average worst itch score (WI-NRS) of ≥7, minimum of 20 PN lesions, and a history of failing a 2-week course of medium to very high potency TCS or ineligible for TCS therapy. Background therapy including low to medium potency TCS or topical calcineurin inhibitors were allowed to be used throughout the trial. The trials excluded patients with PN secondary to medications, other medical conditions, or uncontrolled thyroid disease. At baseline, the mean WI-NRS was 8.5 (severe pruritis), 66% of participants had 20 - 100 nodules (moderate), and 34% had greater than 100 nodules (severe). Less than half of the participants (43%) had a history of atopy (medical history of AD, allergic rhinitis, asthma, or food allergy). The primary endpoint assessed improvement in WI-NRS score ≥4 from baseline at 12-weeks (PRIME2) and 24-weeks (PRIME2). Key secondary outcomes assessed pruritic improvement and reduction in PN lesions (clear skin) as measured by the Investigator's Global Assessment PN-Stage [IGA PN-S] 0-4 scale. Both primary and key secondary endpoints were met as patients on dupilumab (Dupixent) experienced an improvement in itch reduction and skin clearing compared to placebo. No new safety signals were discovered, and adverse effects were consistent with the established safety profile of dupilumab (Dupixent).

	PRIME		**PRIME2**	
	Dupilumab (n=75)	Placebo (n=76)	Dupilumab (n=78)	Placebo (n=82)
% patients with improvement (reduction) in WI-NRS* by ≥4 points from baseline at week 12	44%	16%	37%	22%
% patients with improvement (reduction) in WI-NRS* by ≥4 points from baseline at week 24	60%	18%	58%	20%
% patients with IGA PN-S† 0 or 1 at week 24	48%	18%	45%	16%
**Worst itch score (WI-NRS) is a patient-reported outcome comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch")*				
†The Investigator's Global Assessment PN-Stage (IGA PN) is a clinician-reported outcome assess the activity of PN (IGA PN-A) using a 5-point scale from 0 (clear) to 4 (severe)				

VIII. **Chronic obstructive pulmonary disease (COPD)**

- Dupilumab (Dupixent) was studied in a Phase 3 multicenter, international, double-blind, randomized, placebo-controlled, parallel groups (2 groups), 52-week trial, known as the BOREAS trial, as add-on maintenance treatment for adults with chronic obstructive pulmonary disease (COPD) associated with history of exacerbations and eosinophilic phenotype.
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 report mentioned the trial and stated the findings are potentially important and clinical practice changing but require confirmation in further studies.
- BOREAS trial
  i. Patients enrolled were between ages 40-80 with moderate to severe COPD, blood eosinophils ≥300 cells/µL, smoking history of ≥10 pack-years (current smokers capped at 30%), MRC Dyspnea Scale grade ≥2, documented history of high exacerbation risk, background triple therapy (ICS+LAMA+LABA) [unless ICS was contraindicated] for 3 months, and signs and symptoms of chronic bronchitis for 3 months. Patients were randomized 1:1 to receive either dupilumab (Dupixent) 300 mg every other week (Q2W) or placebo. The primary endpoint was annualized rate of moderate or severe exacerbations of COPD in patients receiving dupilumab or placebo, which was 0.78 (95% CI, 0.64 to 0.93) and 1.10 (95% CI, 0.93 to 1.30), respectively. Rate ratio compared to placebo was 0.70 (95% CI 0.58 to 0.86, p <0.001).
- The BOREAS trial included patients who were 40-80 years of age. The safety and efficacy of dupilumab (Dupixent) has not been studied in pediatric patients less than 18 years of age. There is currently insufficient evidence to support the use of dupilumab (Dupixent) in patients who are less than 18 years of age.
- The BOREAS trial studied dupilumab (Dupixent) in patients with moderate to severe COPD with eosinophilic phenotype, as defined by GOLD guidelines (GOLD 2 or 3). There is currently insufficient evidence to support the use of dupilumab (Dupixent) for mild or very severe COPD (GOLD 1 or 4) and COPD without eosinophilic phenotype.
  i. According to the GOLD 2024 report, the standard grading of severity of COPD is as follows:

Grade	Severity	FEV1 % predicted
GOLD 1	Mild	≥80
GOLD 2	Moderate	50-79
GOLD 3	Severe	30-54
GOLD 4	Very Severe	<30

- Patients in the BOREAS trial were required to have had ≥2 moderate or ≥1 severe exacerbation within the last 12 months. This criterion would place patients in COPD treatment Group E per GOLD 2024 guidelines. These is currently insufficient evidence to support the use of dupilumab (Dupixent) in patients in COPD treatment group A or B, defined by 0 or 1 moderate exacerbations.
- The BOREAS trial studied dupilumab (Dupixent) as add-on treatment for patients already established on background triple inhaler therapy (LAMA+LABA+ICS), unless ICS was contraindicated. Background triple inhaler therapy (LAMA+LABA+ICS) is first-line recommended treatment for Group E COPD patients.

- Per the GOLD 2024 report, background triple inhaler therapy (LAMA+LABA+ICS) has been shown to improve lung function, patient reported outcomes, reduce exacerbations, and improve mortality in patients with COPD. There is currently insufficient evidence to support the use of dupilumab (Dupixent) as monotherapy or with single inhaler therapy.

V. **Chronic Spontaneous Urticaria (CSU)**

- Previously known as chronic idiopathic urticaria (CIU), dupilumab (Dupixent) is the second FDA-approved therapy for CSU, following omalizumab (Xolair). The FDA issued a complete response letter (CRL) for additional efficacy data to support the use of dupilumab (Dupixent) for the treatment of CSU in October 2023. There were no concerns regarding dupilumab's safety or manufacturing process at the time. Updated efficacy and safety data from a third phase 3 trial, in biologic-naïve patients with CSU uncontrolled by antihistamines was resubmitted and accepted for approval in May 2025.
- Per the EAACI/GA²LEN/EDF/WAO guidelines for the definition, classification, diagnosis, and management of urticaria first line treatment for CSU is a 2nd generation H1-antihistamine. If there is inadequate control or response, then it is recommended to increase the 2nd generation H1-antihistamine dose up to 4x the standard dose. If there is no adequate response to the high dose 2nd generation H1-antihistamine after 2-4 weeks, then adding omalizumab (Xolair) 300 mg every 4 weeks is recommended. The guidelines also state that H2-antihistamines (e.g. ranitidine) and leukotriene receptor antagonist (e.g. montelukast) may be alternative treatment options for certain clinical scenarios.
- Per the JTFPP guidelines on the diagnosis and management of acute and chronic spontaneous urticaria it is recommended that first line treatment to be with a 2nd generation H1-antihistamine and the avoidance of triggers (e.g. NSAIDs). If symptoms are still uncontrolled then second line treatment can be one or more of the following: dose advancement of 2nd generation H1-antihistamine, add another second-generation antihistamine, add a H2-antihistamine, add a leukotriene receptor antagonist, or add a 1st generation antihistamine to be taken at bedtime.
- Approval for dupilumab (Dupixent) was evaluated in two 24-week, placebo-controlled, multiple-dose clinical trials, Study (A) (n=136) and Study (C) (n=148). These studies included adult and pediatric patients aged 12 years and older who were symptomatic despite use of antihistamines and assess dupilumab as add-on therapy with antihistamines vs. antihistamines alone. The primary endpoint was the change in weekly itch severity and urticaria activity (ISS7). The primary and all key secondary endpoints significantly favored dupilumab (Dupixent). Study B (n=108) provided additional safety data and evaluated dupilumab (Dupixent) in patients aged 12 years and older who were inadequate responders or intolerant to anti-IgE therapy (omalizumab). The efficacy of dupilumab (Dupixent) was only based on CUPID Study A and C, as study B did not meet statistical significance for reduction in the primary endpoint of ISS7 at week 24. Safety results were generally consistent with the known safety profile of dupilumab (Dupixent) in its approved indications, with the most common adverse effect (>2%) being injection site reactions.
- Both medications, dupilumab (Dupixent) and omalizumab (Xolair) are FDA-approved for CSU, with similar safety and efficacy data to support their use. There

are no head-to-head trials comparing dupilumab (Dupixent) to omalizumab (Xolair) in CSU. Guidelines have consensus regarding the use of omalizumab (Xolair); however, there is no consensus on the use of dupilumab (Dupixent) due to the newer approval.

VI. **Bullous pemphigoid (BP)**

- Dupilumab (Dupixent) received FDA approval for treatment of bullous pemphigoid (BP) in June 2025. Bullous pemphigoid (BP) is a chronic, debilitating, and relapsing rare skin disease affecting approximately 27,000 adults in the U.S. Bullous pemphigoid (BP) primarily affects elderly patients, and is characterized by intense itch, painful blisters, and lesions, as well as reddening of the skin. The blisters and rash can form over much of the body and cause the skin to bleed and break down, resulting in patients being more prone to infection and affecting their daily functioning. The 2022 Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV) recommend topical and oral corticosteroids as first line treatment for BP. The guidelines have not been updated to include dupilumab (Dupixent), but dupilumab (Dupixent) joins doxycycline, dapsone, methotrexate, mycophenolate, and azathioprine as second line treatment or beyond.
- Dupilumab (Dupixent) was studied in a randomized, double-blinded, placebo-controlled Phase 2/3 trial. Participants 18 – 90 years old with confirmed moderate to severe BP via histopathologic, immunopathologic or serologic tests were included in the trial. Participants with other pemphigoid diseases or prior treatment with anti-IL-4 or IL-13 antagonists were not included. Participants were randomized to receive dupilumab (Dupixent) loading dose (600mg once), then 300mg subcutaneously every other week or placebo for 52 weeks. All participants were on standard of care corticosteroids (prednisone or prednisolone) with the intent of tapering off the corticosteroid by week 16. Baseline characteristics were similar between both groups with a mean age of 71.3 years; 53% female; 68% White, 63% of subjects had prior systemic corticosteroid use, and mean peak pruritis NRS was 7.5 (severe). Rescue therapy with high potency topical corticosteroids, oral corticosteroids, systemic non-steroidal immunosuppressive medications, or immunomodulating biologics were administered if needed, however these participants were considered treatment failures.
- The trial demonstrated that dupilumab (Dupixent) was able to achieve the primary outcome of sustained disease remission in 18.3% of participants compared to placebo with a sustained disease remission rate of 6.1% (difference 12.2%, p-0.0114, 95% CI -0.8 to 26.1). A total of 53% in the dupilumab (Dupixent) group and 79% in the placebo group received rescue therapy during the 36-week treatment period. A total of 38.3% of patients achieved ≥4-point itch reduction compared to 10.5% and the median cumulative OCS dose was 2.8 grams compared to 4.1 grams, in the dupilumab (Dupixent) and placebo groups, respectively. The most common adverse events (≥2%) more frequently observed in patients on dupilumab (Dupixent) compared to placebo were arthralgia, conjunctivitis, blurred vision, herpes viral infections, and keratitis. There was one case of acute generalized exanthematous pustulosis in one patient treated with dupilumab (Dupixent) and zero patients treated with placebo. There are some minor applicability concerns (i.e. mild BP was not included in the trial and efficacy in this population is unknown) and limitations such as low number of participants and unknown

concealment and censoring methods, but none that are lethal to the validity of the trial results.

Investigational or Not Medically Necessary Uses

I. Dupilumab (Dupixent) is and has been studied in a variety of other conditions, there is currently insufficient evidence to support the use of dupilumab (Dupixent) outside of the FDA approved indications.

Appendix

I. Table 1: Topical Corticosteroid Potency Chart[12]

Potency Group	Corticosteroid	Vehicle type/form	Brand names	Available strength(s), percent (except as noted)
Super-high potency (Group 1)	Betamethasone dipropionate, augmented	Gel, lotion, ointment (optimized)	Diprolene	0.05
	Clobetasol propionate	Cream, gel, ointment, solution (scalp)	Temovate	0.05
		Cream, emollient base	Temovate E	0.05
		Lotion, shampoo, spray aerosol	Clobex	0.05
		Foam aerosol	Olux-E, Tovet	0.05
		Solution (scalp)	Cormax	0.05
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm2
	Halobetasol propionate	Cream, lotion, ointment	Ultravate	0.05
High potency (Group 2)	Amcinonide	Ointment	Cyclocort¶, Amcort¶	0.1
	Betamethasone dipropionate	Ointment	Diprosone¶	0.05
		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Clobetasol propionate	Cream	Impoyz	0.025
	Desoximetasone	Cream, ointment, spray	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon¶, Florone¶	0.05
		Cream, emollient	ApexiCon E	0.05
	Fluocinonide	Cream, gel, ointment, solution	Lidex¶	0.05
	Halcinonide	Cream, ointment, solution	Halog	0.1
	Halobetasol propionate	Lotion	Bryhali	0.01
High potency (Group 3)	Amcinonide	Cream	Cyclocort¶, Amcort¶	0.1
		Lotion	Amcort¶	0.1

	Betamethasone dipropionate	Cream, hydrophilic emollient	Diprosone¶	0.05
	Betamethasone valerate	Ointment	Valisone¶	0.1
		Foam	Luxiq	0.12
	Desoximetasone	Cream	Topicort LP¶	0.05
	Diflorasone diacetate	Cream	Florone¶	0.05
	Diflucortolone valerate (not available in United States)	Cream, oily cream, ointment	Nerisone (Canada, United Kingdom, others)	0.1
	Fluocinonide	Cream aqueous emollient	Lidex-E¶	0.05
	Fluticasone propionate	Ointment	Cutivate	0.005
	Mometasone furoate	Ointment	Elocon	0.1
	Triamcinolone acetonide	Cream, ointment	Aristocort HP¶, Kenalog¶, Triderm	0.5
Medium potency (Group 4)	Betamethasone dipropionate	Spray	Sernivo	0.05
	Clocortolone pivalate	Cream	Cloderm	0.1
	Fluocinolone acetonide	Ointment	Synalar¶	0.025
	Flurandrenolide	Ointment	Cordran	0.05
	Hydrocortisone valerate	Ointment	Westcort	0.2
	Mometasone furoate	Cream, lotion, ointment, solution	Elocon¶	0.1
	Triamcinolone acetonide	Cream	Kenalog¶, Triderm	0.1
		Ointment	Kenalog¶	0.1
		Ointment	Trianex	0.05
		Aerosol spray	Kenalog	0.2 mg per 2 second spray
		Dental paste	Oralone	0.1
Lower-mid potency (Group 5)	Betamethasone dipropionate	Lotion	Diprosone¶	0.05
	Betamethasone valerate	Cream	Beta-Val, Valisone¶	0.1
	Desonide	Ointment	DesOwen, Tridesilon¶	0.05
		Gel	Desonate	0.05
	Fluocinolone acetonide	Cream	Synalar¶	0.025
	Flurandrenolide	Cream, lotion	Cordran	0.05
	Fluticasone propionate	Cream, lotion	Cutivate	0.05
	Hydrocortisone butyrate	Cream, lotion, ointment, solution	Locoid, Locoid Lipocream	0.1
	Hydrocortisone probutate	Cream	Pandel	0.1

	Hydrocortisone valerate	Cream	Westcort¶	0.2
	Prednicarbate	Cream (emollient), ointment	Dermatop	0.1
	Triamcinolone acetonide	Lotion	Kenalog¶	0.1
		Ointment	Kenalog¶	0.025
Low potency (Group 6)	Alclometasone dipropionate	Cream, ointment	Aclovate	0.05
	Betamethasone valerate	Lotion	Beta-Val¶, Valisone¶	0.1
	Desonide	Cream	DesOwen, Tridesilon¶	0.05
		Lotion	DesOwen, LoKara	0.05
		Foam	Verdeso	0.05
	Fluocinolone acetonide	Cream, solution	Synalar¶	0.01
		Shampoo	Capex	0.01
		Oil (48% refined peanut oil)	Derma-Smoothe/FS Body, Derma-Smoothe/FS Scalp	0.01
	Triamcinolone acetonide	Cream, lotion	Kenalog¶, Aristocort¶	0.025
Least potent (Group 7)	Hydrocortisone (base, ≥2%)	Cream, ointment	Hytone, Nutracort¶	2.5
		Lotion	Hytone, Ala Scalp, Scalacort	2
		Solution	Texacort	2.5
	Hydrocortisone (base, <2%)	Ointment	Cortaid, Cortizone 10, Hytone, Nutracort	1
		Cream	Cortaid¶, Cortizone 10, Hytone, Synacort	1
		Gel	Cortizone 10	1
		Lotion	Aquanil HC, Sarnol-HC, Cortizone 10	1
		Spray	Cortaid	1
		Solution	Cortaid, Noble, Scalp Relief	1
		Cream, ointment	Cortaid	0.5
	Hydrocortisone acetate	Cream	MiCort-HC	2.5
		Lotion	Nucort	2

¶ Inactive United States brand name for specific product; brand may be available outside United States

II. Abbreviated list of H1 antihistamine products:

*H1 Antihistamine Products (not all inclusive)	

• fexofenadine • loratadine • desloratadine • cetirizine • levocetirizine • clemastine • diphenhydramine	• chlorpheniramine • hydroxyzine • cyproheptadine • brompheniramine • triprolidine • dexchlorpheniramine • carbinoxamine

References

1. Dupixent [Prescribing Information]. Tarrytown, NY and Bridgewater, NJ: Regeneron Pharmaceuticals, Inc and Sanofi Genzyme. June 2025.
2. Sidbury R, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. J Am Acad Dermatol 2014;71:1218-1233.
3. Wollenberg A, et al. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. JEADV 2016;30:729-747.
4. UpToDate, Inc. Management of severe refractory atopic dermatitis (eczema). UpToDate [database online]. Waltham, MA. Updated Dec 2016. Accessed January 18, 2017.
5. Totri CR, et al. Prescribing practices for systemic agents in the treatment of severe pediatric atopic dermatitis in the US and Canada: the PeDRA TREAT survey. J Am Acad Dermatol. 2017 Feb;76(2):281-285.
6. Solomon, CG and Hopkins C. Chronic Rhinosinusitis with Nasal Polyps. N Engl J Med 2019;381:55-63
7. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical Practice Guideline (Update): Adult Sinusitis. American Academy of Otolaryngology – Head and Neck Surgery 2015, Vol.I52(2S) SI-S39.
8. Institute for Clinical and Economic Review (ICER): Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks. December 2018. Available at: https://icer-review.org/wp-content/uploads/2018/04/ICER_Asthma_Final_Report_122018-1.pdf
9. Institute for Clinical and Economic Review (ICER): Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. June 2017. Available at: https://icer-review.org/wp-content/uploads/2016/10/MWCEPAC_ATOPIC_FINAL_EVIDENCE_REPORT_060717.pdf
10. Simpson EL, Paller AS, Siegfried EC et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis a phase 3 randomized clinical trial. JAMA Dermatol 2020;156(1):44-56. Available from: https://pubmed.ncbi.nlm.nih.gov/31693077/
11. Paller AS, Siegfried EC, Thaci D et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double blinded, placebo-controlled phase 3 trial. J Am Acad Dermatol 2020; S0190-9622(20)31152-X. Available from: https://pubmed.ncbi.nlm.nih.gov/32574587/
12. UpToDate, Inc. Topical corticosteroids: Use and adverse effects. UpToDate [database online]. Waltham, MA. Updated Feb 2020. Accessed March 12, 2021.
13. National Insititute for Health and Care Excellence (NICE). Dupilumab for treating moderate to severe atopic dermatitis. NICE. Published August 1, 2018.
14. UpToDate, Inc. Clinical manifestations and diagnosis of eosinophilic esophagitis (EoE). UpToDate [database online]. Waltham, MA. Updated Jun 2022. Accessed July 11, 2022.
15. UpToDate, Inc. Dietary management of eosinophilic esophagitis. UpToDate [database online]. Waltham, MA. Updated Aug 2020. Accessed July 11, 2022.
16. UpToDate, Inc. Treatment of eosinophilic esophagitis. UpToDate [database online]. Waltham, MA. Updated Jun 2022. Accessed July 11, 2022.
17. Hirano I, Chan ES, Rank MA, et al. AGA Institute and the Joing Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. *Gastroenterology*. 2020;158:1776-1786.
18. Dellon et al. Updated international consensus diagnostic criteria for eosinophilic esophagitis: Proceedings of the AGREE conference. *Gastroenterology*. 2018 October; 155(4):1022-1033.
19. Dellon et al. Dupilumab Improves Clinical and Histologic Aspects of Disease in Adult and Adolescent Patients with Eosinophilic Esophagitis at Week 24: Weekly and Every 2 Weeks' Results from Part B of the 3-Part Liberty EoE TREET Study. Poster. 2021.
20. Dellon et al. The Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis: Results from Part A of a Randomized, Placebo-Controlled Three-Part, Phase 3 Study. Poster presented at the 34th Annual Eastern Allergy Conference; Palm Beach, FL; June 2021.

21. Study of dupilumab for the treatment of patients with prurigo nodularis, inadequately controlled on topical prescription therapies or when those therapies are not advisable (LIBERTY-PN PRIME). ClinicalTrials.gov identifier: NCT04183335. February 17, 2022. Accessed October 10, 2022. https://clinicaltrials.gov/ct2/show/NCT04183335.
22. Study of dupilumab for the treatment of patients with prurigo nodularis, inadequately controlled on topical prescription therapies or when those therapies are not advisable (PRIME2). ClinicalTrials.gov identifier: NCT04202679. September 28, 2022. Accessed October 10, 2022. https://clinicaltrials.gov/ct2/show/NCT04202679
23. Elmariah S, Kim B, Berger T, et al. Practical approaches for diagnosis and management of prurigo nodularis: United States expert panel consensus. *J Am Acad Dermatol*. 2021;84(3):747-760. doi:10.1016/j.jaad.2020.07.025
24. Ständer HF, Elmariah S, Zeidler C, et al. Diagnostic and treatment algorithm for chronic nodular prurigo. *J Am Acad Dermatol*. 2020;82(2):460-468. doi:10.1016/j.jaad.2019.07.022
25. Ständer S, Pereira MP, Berger T, et al. IFSI-guideline on chronic prurigo including prurigo nodularis. *Itch*. 2020;5(4):e42-e42.
26. Pereira MP, Steinke S, Zeidler C, et al. European academy of dermatology and venereology European prurigo project: expert consensus on the definition, classification and terminology of chronic prurigo. *J Eur Acad Dermatol Venereol*. 2018;32(7):1059-1065.
27. UpToDate, Inc. Prurigo nodularis. UpToDate [database online]. Waltham, MA. Updated May 2022. Accessed October 10, 2022.
28. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023;389(3):205-214. doi:10.1056/NEJMoa2303951
29. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global Initiative for Chronic Obstructive Lung Disease 2024 Report. Global Initiative for Chronic Obstructive Lung Disease; 2024.
30. Rank MA, Chu DK, Bognanni A, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. *Journal of Allergy and Clinical Immunology*. 2023;151(2):386-398.
31. Orlandi RR, Kingdom TT, Smith TL, et al. International consensus statement on allergy and rhinology: rhinosinusitis 2021. International Forum of Allergy & Rhinology. 2021;11(3):213-739.
32. UpToDate, Inc. Chronic rhinosinusitis with nasal polyposis: Management and prognosis. UpToDate [database online]. Waltham, MA. Updated August 2023. Accessed October 1, 2024.
33. Maurer M, Casale TB, Saini SS, et al. Dupilumab in patients with chronic spontaneous urticaria (LIBERTY-CSU CUPID): Two randomized, double-blind, placebo-controlled, phase 3 trials. J Allergy Clin Immunol. 2024;154(1):184-194. doi:10.1016/j.jaci.2024.01.028Title
34. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-766. doi:10.1111/all.15090Organization and Title
35. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. J Allergy Clin Immunol. 2014;133(5):1270-1277. doi:10.1016/j.jaci.2014.02.036
36. Borradori L, Van Beek N, Feliciani C, et al. Updated S2 K guidelines for the management of bullous pemphigoid initiated by the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2022;36(10):1689-1704.
37. Murrell DF, Joly P, Werth VP, et al. Study Design of a Phase 2/3 Randomized Controlled Trial of Dupilumab in Adults with Bullous Pemphigoid: LIBERTY-BP ADEPT. Adv Ther. 2024;41(7):2991-3002.

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
omalizumab (Xolair)	Allergic asthma
	Chronic rhinosinusitis with nasal polyposis (CRSwNP)
	Chronic spontaneous urticaria (CSU)
	Systemic Mastocytosis
Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease	Atopic dermatitis
ruxolitinib (Jakafi, Opzelura)	Atopic dermatitis
tralokinumab (Adbry)	Atopic dermatitis
tapinarof (Vtama)	Atopic dermatitis
Lebrikizumab (Ebglyss)	Atopic dermatitis
ensifentrine (Ohtuvayre)	Chronic Obstructive Pulmonary Disease (COPD)

benralizumab (Fasenra Pen)	Asthma (severe)
tezepelumab (Tezspire)	Asthma (severe)
mepolizumab (Nucala)	Asthma (severe)
	Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
	Chronic Obstructive Pulmonary Disease (COPD)
reslizumab (Cinqair)	Asthma (severe)

Policy Implementation/Update

Action and Summary of Changes	Date
Added new indication of bullous pemphigoid (BP) and supporting evidence. Updated QL table, supporting evidence, E/I, references.	09/2025
Add new indication and supporting evidence for Dupixent in the setting of CSU. Updated QL table, supporting evidence, E/I, references, appendix tables, and related policies.	07/2025
Removed oral steroid trial from CRSwNP indication. Updated patient weight for EoE.	03/2025
Updated age criteria in CRSwNP to reflect age expansion to patients 12 years of age or older. Updated supporting evidence, references, related policies. Updated definition/examples of moderate to severe disease in prurigo nodularis. Updated initial criteria to 12 months for all policy listed indications.	10/2024
Added new indication and supporting evidence for Dupixent in the setting of COPD (live 10/24/24). Updated references and listed E/I for use in COPD for pediatric patients <18 years of age.	07/2024
Updated age criteria in eosinophilic esophagitis for the newly FDA approved indication in those one year and older. Updated supporting evidence and references.	02/2024
Review conducted. Update to supporting evidence.	02/2023
Added new indication and supporting evidence for Dupixent in the setting of prurigo nodularis. Added related pruritic conditions (urticaria, bullous pemphigoid/prurigo, etc.) to E/I. Updated references. Added related policies section.	10/2022
Added criteria and supporting evidence for new FDA-approved indication for eosinophilic esophagitis; Updated age criteria in atopic dermatitis to reflect FDA-approved age expansion from age 6 years to age 6 months and older	08/2022
Updated age criteria in asthma to reflect FDA extended indication from age 12 now to age 6 and older; updated QL table to include dosing for Atopic Dermatitis and comorbid Atopic Dermatitis and Severe to Moderate Asthma	11/2021
Added 200 mg/1.14mL pen injector; Updated to allow 12-month approval for initial therapy	07/2021
Updated Policy. Atopic dermatitis: combined pediatric and adolescent/adult criteria; updated BSA criterion and Group 1 corticosteroids. Asthma: updated criteria defining moderate or severe asthma; updated eosinophilic phenotype criterion; defined exacerbation criterion; revised maintenance treatment requirements; removed environmental trigger criterion. CRSwNP: revised diagnosis criteria to include provider attestation; updated treatment history to one intranasal corticosteroid and one OCS therapy. Renewal criteria: added standard renewal criteria documenting patient establishing treatment; added criterion excluding concomitant MCA use.	04/2021
Updated QL table to include pediatric dosing in AD	01/2021
Criteria update: updated age criteria to reflect newly FDA approved extended indication for atopic dermatitis use from 12 years of age to expanded use in pediatrics aged six to 11 years of age. Removal of PGA score as a requirement option with BSA in atopic dermatitis.	10/2020
Criteria was transitioned to policy format with the addition of supporting evidence and a section for investigation/not medically necessary usage. Addition of newly FDA approved age expansion for atopic dermatitis from 18 years of age to 12 years of age. Also, addition of newly FDA approved indication for chronic rhinosinusitis with nasal polyposis along with criteria for approval based on guidelines and clinical trials review. Lastly, the duration of initial approval has been increased form 3 months to 6 months based on evidence from ICER reports and the study design of the most recent FDA approved indication for chronic rhinosinusitis with nasal polyposis.	08/2019
Criteria update: Incorporated new diagnosis of moderate to severe asthma and appropriate criteria	12/2018
Updated format and added the renewal approval duration	01/2018
Criteria update: excluded samples and updated renewal language to general improvement	04/2017

duvelisib (Copiktra®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP222

Split Fill Management*

Description

Duvelisib (Copiktra) is an orally administered inhibitor of phosphoinositide 3-kinase (PI3K) with inhibitory activity predominantly against PI3K-δ and PI3K-γ isoforms expressed in normal and malignant B-cells.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
duvelisib (Copiktra)	15 mg capsules	Relapsed/refractory chronic lymphocytic leukemia (CLL); Relapsed/refractory small lymphocytic lymphoma (SLL);	56 capsules/28 days
	25 mg capsules		

Initial Evaluation

I. Duvelisib (Copiktra) 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. Member does not have a history of histological transformation (HT); **AND**
   D. Not used in combination with any other oncology therapy; **AND**
   E. Member has not progressed while on therapy with another PI3K inhibitor [e.g. copanlisib (Aliqopa), idelalisib (Zydelig)]; **AND**
   F. A diagnosis of **relapsed/refractory chronic lymphocytic leukemia (CLL) OR relapsed/refractory small lymphocytic lymphoma (SLL)** when the following are met:
      i. Treatment with one of the following has been ineffective or not tolerated or BOTH have been contraindicated:
         a. Bruton tyrosine kinase (BTK) inhibitor [e.g. ibrutinib (Imbruvica), acalabrutinib (Calquence)] **OR**
         b. BCL2 inhibitor [e.g. venetoclax (Venclexta)]; **AND**
      ii. Treatment with at least **ONE** of the following additional therapies has been ineffective, not tolerated, or ALL are contraindicated:
         a. fludarabine/cyclophosphamide/rituximab (FCR)
         b. alkylating agent (e.g., chlorambucil, bendamustine, cyclophosphamide)

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

c. monoclonal antibody (e.g., ofatumumab, rituximab, obinutuzumab)
d. purine analog (e.g., fludarabine, pentostatin, cladribine)

II. Duvelisib (Copiktra) is considered investigational when used for all other conditions, including but not limited to:
   A. Relapsed/refractory follicular lymphoma (FL)
   B. Head and Neck Cancer
   C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome
   D. Moderate to Severe Rheumatoid Arthritis
   E. Coronavirus Infection (COVID-19)

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. Disease response to treatment defined by stabilization of disease or improvement in disease or disease symptoms.

Supporting Evidence

I. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory CLL/SLL has been studied in a global, multicenter, randomized, open-label, Phase 3, superiority trial in 319 adult patients.
   - The two treatment arms included the duvelisib (Copiktra) and ofatumumab arm. Treatment groups were balanced, had a median number of prior therapies of two with approximately one-third having received three or more prior lines of therapy. Most patients had previously received an alkylating agent (chlorambucil, bendamustine, cyclophosphamide) 93% in the duvelisib (Copiktra) and 95% in the ofatumumab group, a monoclonal antibody (ofatumumab, rituximab, obinutuzumab) 78% in the duvelisib (Copiktra) and 83% in the ofatumumab group, and purine analog (60% duvelisib (Copiktra); 71% ofatumumab).
   - The primary endpoint of Progression-free Survival (PFS) was significantly longer for the duvelisib (Copiktra) arm compared with the ofatumumab arm (13.3 months vs 9.9 months, HR = 0.52, P < 0.0001).
   - The key secondary endpoint of Overall Response Rate (ORR) was also significantly higher compared with ofatumumab (73.8% vs 45.3%; P < 0.0001), but the OS was not statistically different and the median overall survival (OS) was not reached on either treatment arm with a 12-month probability of survival of 86% (HR = 0.99; 95% CI, 0.65-

1.50) for both treatments. This could be due to the availability of multiple CLL therapies to rescue patients on either arm following disease progression, including administration of duvelisib in a separate, optional extension study to 89 patients who had confirmed progressive disease on ofatumumab in the DUO study.

- Almost all patients in the study experienced an AE, 124 duvelisib (Copiktra)-treated patients had discontinued treatment, with the most common reasons being AEs (35%), disease progression (22%), subject withdrawal (8%), and death (8%).
- Fatal adverse reactions within 30 days of the last dose occurred in 36 patients (8%) treated with duvelisib (Copiktra) 25 mg twice daily. Serious adverse reactions were reported in 289 patients (65%). The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%), most often due to diarrhea or colitis, infection, and rash. Duvelisib (Copiktra) was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The median time to first dose modification or discontinuation was 4 months (range: 0.1 to 27), with 75% of patients having their first dose modification or discontinuation within 7 months.

II. Histological transformation (HT) refers to the evolution of a clinically indolent disease (e.g. FL) to a clinically aggressive disease [e.g. diffuse large B-cell lymphoma (DLBCL)] defined as those lymphomas in which survival of the untreated patient is measured in months. The HT that occurs in patients with CLL/SLL has been termed Richter's transformation. When histological transformation is present, these patients are generally treated differently than their primary diagnosis. The goal of therapy for most patients is to eliminate the aggressive component of the disease (i.e. the histologically transformed cells) while minimizing toxicity. The most common treatment regimens for patients with HT include conventional chemotherapy with immunotherapy and high dose therapy followed by hematopoietic cell transplantation. There is no clinical trial data to support the use of duvelisib (Copiktra) in patients with HT.

III. Per the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, CLL/SLL, recognizes duvelisib (Copiktra) as a preferred regimen for r/r CLL/SLL (Category 2A recommendation). Ibrutinib (Imbruvica), acalabrutinib (Calquence), venetoclax (Venclexta) plus rituximab are Category 1 recommendation, based on the results of the Phase 3 randomized studies (ASCEND, RESONATE and MURANO, respectively). Idelalisib (Zydelig) plus rituximab and duvelisib (Copiktra) are also preferred regimens in these populations with a category 2A recommendation due to their toxicity profile (colitis, diarrhea, and increased risk of infections).

Investigational or Not Medically Necessary Uses

I. Duvelisib (Copiktra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Relapsed/refractory follicular lymphoma (FL)
      i. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory FL has been studied in a single-arm, Phase 2, open-label study in 129 patients.

- Duvelisib (Copiktra) 25 mg twice daily was administered in patients with FL (N = 83) who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. Patients were refractory to rituximab either alone or in combination (127 patients [98%]), 119 patients (92%) had disease refractory to an alkylating agent or purine analog, and 117 patients (91%) had disease refractory to combination therapy with rituximab and an alkylating agent.
- Patients had a median of three prior lines of therapy (range: 1 to 10), and 40% receiving four or more prior regiments, with 94% being refractory to their last therapy and 81% being refractory to 2 or more prior lines of therapy.
- The primary endpoint was met with Overall Response Rate (ORR) being 47% (95% CI, 38% to 56%). The key secondary endpoint of duration of response (DOR was 10 months (95% CI, 6.5 to 10.5 months)
- Due to treatment emergent adverse events (TEAE), forty patients (31%) discontinued duvelisib (Copiktra). In 85 (66%) of patients TEAEs were managed with dose interruption or reduction.
- The most frequent grade 3 or greater TEAEs were neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%). Seventeen deaths (13.2%) occurred on treatment

ii. Almost all patients in the study assessing the safety and efficacy of duvelisib (Copiktra) were refractory to rituximab (98.4%), alkylating agent/purine analog (92.2%) and alkylating agent (90.7%).

iii. The NCCN B-cell Lymphomas guideline set duvelisib (Copiktra) as a second-line therapy for FL that is relapsed or refractory to at least two prior therapies, a category 2A recommendation. Anti–CD20 antibody–based chemoimmunotherapy [e.g., obinutuzumab (Gazyva), ofatumumab (Arzerra)] is the standard initial treatment for newly diagnosed and relapsed/refractory FL. Options for treatment at first relapse include alternate non–cross-resistant chemoimmunotherapy regimens or combination lenalidomide + rituximab. Rituximab monotherapy may be appropriate for patients with late relapse as well, particularly if disease burden is low.

iv. Patients with Grade 3b FL were excluded from the clinical trial. Grade 3b FL is often referred to as follicular large cell lymphoma and patients commonly present with a more clinically aggressive course. It is commonly treated with regimens used for clinically aggressive lymphomas, such as a Diffuse Large B-Cell Lymphoma (DLBCL).

v. Although, the primary outcome of ORR was met, the quality of evidence is low considering the single arm, Phase 2, open-label trial design. Furthermore, patients included in this trial experienced significant TEAEs and limited efficacy. Given these considerations treatment with duvelisib (Copiktra) in the setting of relapsed/refractory follicular lymphoma (FL) is considered experimental/investigational.

B. Head and Neck Cancer

i. A Phase 1b/2, open label, non-randomized, single group study of duvelisib (Copiktra) in combination with pembrolizumab in subjects with recurrent or metastatic head and neck squamous cell cancer is still recruiting.

C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome
   i. A Phase 1 open label, non-randomized, single group study with an expansion cohort of duvelisib (Copiktra) and nivolumab in Mycosis Fungoides (MF) and Sezary Syndrome (SS) is not yet recruiting.

D. Moderate to Severe Rheumatoid Arthritis
   i. A Phase 2, double blind, placebo-controlled, randomized study to evaluate multiple dose levels of duvelisib (Copiktra) with background methotrexate in subjects with active rheumatoid arthritis and an inadequate response to methotrexate alone was completed in 2018 but no results have been published.

E. Coronavirus Infection (COVID-19)
   ii. A Phase 2, double blind, placebo-controlled, randomized study to evaluate whether a two-week exposure to duvelisib (Copiktra), reduces inflammation in the lungs in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 who do not require mechanical ventilation at study initiation. The study is not yet recruiting.

** 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. Copiktra [prescribing information]. Needham, MA: Verastem; September 2018.
2. Flinn, Ian W. et al "The phase 3 DUO trial: duvelisib versus ofatumumab in relapsed and refractory CLL/SLL." Blood (2018): blood-2018-05-850461. Web. 16 Oct. 2018.
3. Flinn, Ian W. et al "Dynamo: A Phase 2 Study Demonstrating the Clinical Activity of Duvelisib in Patients with Relapsed Refractory Indolent Non-Hodgkin Lymphoma." Blood 128.22 (2016): 1218. Web. 16 Oct. 2018
4. Wierda WG, Byrd JC, Abramson JS, et al. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Version 4.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020;18(2):185-217. doi:10.6004/jnccn.2020.0006
5. Zelenetz AD, Gordon LI, Abramson JS, et al. NCCN Guidelines Insights: B-Cell Lymphomas, Version 3.2019. J Natl Compr Canc Netw. 2019;17(6):650-661. doi:10.6004/jnccn.2019.0029
6. Verastem, Inc. A Study of Duvelisib in Combination With Pembrolizumab in Head and Neck Cancer. ClinicalTrials.gov Identifier: NCT04193293
7. National Cancer Institute (NCI). Duvelisib and Nivolumab for the Treatment of Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome. ClinicalTrials.gov Identifier: NCT04652960
8. Verastem, Inc. A Double-Blind Study Evaluating Duvelisib in Subjects With Moderate to Severe Rheumatoid Arthritis and an Inadequate Response to Methotrexate Alone (ASPIRA). ClinicalTrials.gov Identifier: NCT0185170
9. Emory University, Verastem, Inc., University of Pennsylvania. Duvelisib Ameliorates Manifestations of Pneumonia in Established Novel Coronavirus Infection (COVID-19) (DAMPEN-CI). ClinicalTrials.gov Identifier: NCT04487886

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria: age requirement, requirement of monotherapy, requirement of non-progression on a different PI3K inhibitor, requirement of one or more prior therapy if diagnosed with CLL/SLL Removed criteria: requirement for pneumocystis jirovecii pneumonia (PCP) prophylaxis and no history of allogenic stem cell transplant Moved the follicular lymphoma indication to investigational uses Criteria updated to policy format	2/2021
Policy created	11/2018

edaravone (Radicava ORS®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP263

Description

Edaravone (Radicava ORS) is an orally administered free radical scavenger.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
edaravone (Radicava ORS)	Amyotrophic Lateral Sclerosis (ALS)	105mg/ 5mL starter kit	70mL/28 days
		105mg/ 5mL suspension	50mL/28 days

Initial Evaluation

I. **Edaravone (Radicava ORS)** 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)** when the following are met:
      1. Provider attestation that the member has a diagnosis of ALS (e.g., clinically definite, probable ALS, bulbar ALS, etc.); **AND**
      2. Member has a disease duration of 2 years or less since diagnosis; **AND**
      3. Provider attestation that the member does NOT have advanced disease [note: advanced disease may include loss of multiple physical functionalities such as ability to swallow, walk, speak, dress/groom, etc.]; **AND**
      4. Member does not require permanent mechanical ventilation by intubation or tracheostomy; **AND**
      5. Edaravone (Radicava ORS) will be used in combination with riluzole (Rilutek); **OR**
         i. Treatment with riluzole (Rilutek) has been ineffective, not tolerated, or is contraindicated

II. Edaravone (Radicava) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute Ischemic Stroke

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**

II. Member is changing from edaravone (Radicava) IV therapy to edaravone (Radicava ORS); **AND**
III. 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**
IV. Member does not require permanent mechanical ventilation by intubation or tracheostomy plan; **AND**
V. Provider attestation that edaravone (Radicava ORS) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member

Supporting Evidence

I. Edaravone (Radicava) was only studied in clinical trials in adult patients and efficacy and safety of this drug for the pediatric population is not known. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease and does not show up in younger patients, with the average age of onset being 55 years.
II. ALS is a difficult and complex disease to diagnose and treatment for this disease is specialized and individualized; thus, a specialist provider, or consultation with a specialist (e.g., neurologist), is required.
III. Edaravone (Radicava) was initially approved for IV administration for the treatment of ALS, in a six-month, randomized, placebo-controlled, double-blind study (study 19) of 137 Japanese patients with ALS, who lived independently and had the following baseline criteria: definite or probable ALS diagnosis based on El Escorial revised criteria; disease diagnosed less than 2 years before; normal respiratory function (defined as %FVC >80%); functionality retained in most activities of daily living (defined as scores of 2 points or better on each item of the ALS function rating scale- revised [ALSFRS-R]) with a specific requirement of a score of 4 on dyspnea, orthopnea, and respiratory insufficiency. The primary endpoint was the change in the treatment arms in the ALSFRS-R total scores at baseline and week 24. Majority (≥ 90%) of patients enrolled in each arm were also taking riluzole (Rilutek).
IV. The ALSFRS-R is a 12-item questionnaire assessing functional disease progression across four domains including bulbar, fine motor, gross motor, and respiratory. Each item is scored on a five-point ordinal scale from 0 (loss or significant impairment) up to 4 (normal function) with a possible cumulative score of 48. A score of 2 or better on each item would be a minimum ALSFRS-R score of 24. The ALSFRS-R score correlates to preserved function with a higher score meaning function closer to a normal individual without ALS. Patients with a lower total score are those with advanced disease who have lost function over several of these domains (e.g. lost ability to swallow, walk, speak, dress themselves, grip/hold items); these patients are also associated with worst disease outcomes.
V. The primary efficacy outcome for Study 19 was the change in ALSFRS-R score from baseline to week 24. The change from baseline and at week 24 of the ALSFRS-R score was reported as least-squares mean (LSM) change ± standard error [95 % confidence interval (CI)]. Edaravone (Radicava) had a change of -5.01 ± 0.64 versus -7.50 ± 0.66 for placebo. This correlated with a treatment difference of 2.49 (SE 0.76, 0.99-3.98, 95% CI; *p* 0.0013) in favor of edaravone (Radicava).
VI. Oral edaravone (Radicava ORS) suspension was approved in 2022 in a global, open-label, phase 3 safety study of 185 patients receiving 105mg of edaravone (Radicava) on the same IV dosing

schedule. While patients were included in the study with a baseline FVC of 70 or greater, and a disease diagnosis within 3 years, this study did not evaluate efficacy in these parameters and only assessed safety data. Once again in the ORS study, 87% of patients were also using riluzole (Rilutek). The 105mg oral dose was found in the pharmacokinetic phase 1 trial to provide the same drug exposure as the 60mg-IV formulation.

VII. The IV-edaravone (Radicava) is generally well tolerated with abnormal gait (13%) and bruising (15%) being the most common adverse events, followed by headache (10%), dermatitis/eczema (8/7%), and respiratory concerns (dyspnea, hypoxia, failure 6%). Additionally, Radicava ORS has an incidence of fatigue (7.6%).

VIII. The American Academy of Neurology (AAN) does not provide specific guidance on the use of edaravone (Radicava) in ALS patients. As of November 2022, the guidelines recommend starting riluzole as a first-line therapy upon diagnosis to slow disease progression, and the majority of the guideline centers around palliative care and support. Available clinical data surrounding the efficacy of edaravone (Radicava) is based on the proposed benefit of slowing the progression of disease symptoms but did not exhibit a clear survival benefit.

IX. In an outreach to a key opinion leader (KOL), a neurologist, who has experience in treating ALS patients, the expert noted that there is no formal guidance on the use of edaravone (Radicava) outside of how the medication was studied (i.e. over 80% FVC predicted and ALSFRS-R total starting score of 24, etc.) The expert did note that the FDA has expanded approval to all patients with ALS; however, insurers have mainly adopted criteria to match the clinical trials. The reviewer did note in 2021 there was a recommendation to relax this criterion, but it has not been formally accepted by either the AAN or the American Associated of Neuromuscular and Electrodiagnostic Medicine. Additionally, there was no specific part of the ALSFRS-R score, which may be valued as more of an indicator for disease progression besides those with a bulbar dysfunction (often evidenced in swallowing or speech problems) and that once a diagnosis of ALS has been reached, the offer to use edaravone (Radicava) is presented to all patients.

X. A recent long-term edaravone (Radicava) efficacy in ALS post-hoc analysis of study 19 was published showing edaravone (Radicava) maintained benefits in patients up to one year post the clinical trial versus placebo, as measured by changes (reduction) in the ALSFRS-R scores. However, true long-term benefits of edaravone (Radicava) are still unknown and there is no way to tell if the drug is working individually. In our KOL outreach, the expert noted that once a patient has begun therapy, it is difficult to establish a stopping point. However, it would be rational to stop therapy once the disease has progressed too far along for a benefit, such as the patient being on permanent machinal ventilation.

XI. Proposed therapy pathway and benefits of edaravone are supported by a review from the American Journal of Managed Care, where specialists in ALS supported both an attestation from a neurologist of continued benefit from the drug as a criterion for continuation of edaravone and stopping therapy once invasive ventilation was required. Additionally, during the confirmatory trial for IV-edaravone, therapy was discontinued if the subject required a tracheotomy or all-day respiratory support. The open-label extension trial after study 19 utilized the criterion of discontinuing therapy when the %FVC was < 50% and the P_aCO_2 (blood gas) was ≥ 45mm of Hg. Thus, current clinical data does not support continued benefits of edaravone therapy in patients, who progress to advanced disease and require respiratory interventions.

XII. Edaravone (IV or oral) formulations are expected to serve as an adjunct therapy to first line riluzole and may be utilized by the majority of patients with an initial diagnosis of ALS. Due to the convenience and advantage of oral administration, patients established on IV edaravone may convert to oral edaravone (Radicava ORS) to a higher degree. Additionally, Radicava ORS may also be considered as an initial formulation of choice. For members converting to the oral formulation (Radicava ORS) from the IV- edaravone (Radicava), loading dose is not required (1:1 change based on bioequivalence data).

Investigational or Not Medically Necessary Uses

I. Edaravone (Radicava) is considered investigational for the use of Acute Ischemic Stroke, including when used in combination with dexborneol. At this time, the clinical data is inconclusive and edaravone (Radicava) remains not FDA approved for this indication.

References

1. Edaravone (Radicava) [Prescribing Information]. Mitsubishi Tanabe Pharma Corporation; Jersey City, NJ. Issued 5/2022.
2. Miller, R.G., et al; Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review). Subcommittee of the American Academy of Neurology, January 2020.
3. Genge, Angela MD, FRCP; Pattee, Gary L. MD; Sbue, Gen MD, PhD.; et al. "24-week Results from the MT-1186-A01 Phase 3, open-Label, Multicenter Safety Study of Oral Edaravone in Subjects with Amyotrophic Lateral Sclerosis" Poster Presentation from the 32nd International Symposium of ALS/MND 12/2021.
4. Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017 Jul;16(7):505-512.
5. Xu J, Wang Y, Wang A, Gao Z, et al. Safety and efficacy of Edaravone Dexborneol versus edaravone for patients with acute ischaemic stroke: a phase II, multicentre, randomised, double-blind, multiple-dose, active-controlled clinical trial. Stroke Vasc Neurol. 2019 Apr 22;4(3):109-114. doi: 10.1136/svn-2018-000221. PMID: 31709115; PMCID: PMC6812637.
6. Barrington CJ, Burruano M, Carney C; et al. Addressing the role of edaravone in the management of amyotrophic lateral sclerosis and gaps in care and access: expert panel recommendations. Am J Manag Care. 2021 Aug;27(12 Suppl):S231-S237. doi: 10.37765/ajmc.2021.88732. PMID: 34382759.

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
riluzole (Rilutek®, Tiglutik®, Exervan®)	Amyotrophic Lateral sclerosis (ALS)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP327

Description

Efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo) is a subcutaneously administered human immunoglobin G1 (IgG1)-derived antibody that works by reducing circulating IgG in a patient's blood stream decreasing the autoimmune attack of the postsynaptic membrane in the neuromuscular junction in those with myasthenia gravis and chronic inflammatory demyelinating polyneuropathy.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo)	Generalized Myasthenia Gravis; Chronic inflammatory demyelinating polyneuropathy	1,000mg/5mL / 10,000u/5mL prefilled syringe	20mL/28 days
Provider Administered Agents*			
efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo)	Generalized Myasthenia Gravis; Chronic inflammatory demyelinating polyneuropathy	1,008mg/5.6mL / 11,200u/5.6mL vial*	22.4mL/28 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. Subcutaneous vial is only FDA approved for provider administration.*

Initial Evaluation

I. **Efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. The request is for efgartigimod alpha and hyaluronidase (Vyvgart Hytrulo) prefilled syringe; **AND**
   C. Medication is prescribed by, or in consultation with, a specialist (e.g., neurologist or rheumatologist); **AND**
   D. Member has a diagnosis of one of the following:
      1. **Generalized myasthenia gravis (gMG)**; **AND**
         i. Provider attestation that the member is acetylcholine receptor antibody positive (AChR-AB+); **AND**
         ii. Provider attestation that the member has myasthenia gravis class II to IV (i.e., not defined as ocular myasthenia gravis and not intubated); **AND**
         iii. Member has previously had an inadequate response to pyridostigmine and at least one immunosuppressant therapy (i.e., azathioprine, cyclosporine,

mycophenolate), unless all agents were not tolerated or are contraindicated; **AND**

iv. Member will continue on standard of care therapies (i.e., azathioprine, cyclosporine, mycophenolate); **AND**

v. Member has a baseline Myasthenia Gravis-activities of daily living (MG-ADL) total score of at least 5; **AND**

vi. Medication will **NOT** be used in combination with maintenance immunoglobulin therapy (IVIG), eculizumab (Soliris), ravulizumab (Ultomiris), rozanolixizumab (Rystiggo), zilucoplan (Zilbrysq) or rituximab; **OR**

2. Chronic inflammatory demyelinating polyneuropathy (CIDP); AND

i. Provider attestation that the member has typical chronic inflammatory demyelinating polyneuropathy (CIDP) (characterized by symmetric muscle weakness and sensory loss); **AND**

ii. Documentation of progressing or relapsing disease course based on ONE of the following:

a. Chronic inflammatory demyelinating polyneuropathy (CIDP) disease activity status (CDAS) score of 2 or more; **OR**

b. Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale of 2 more; **AND**

iii. Treatment with immunoglobulin (Ig) has been ineffective, not tolerated, or contraindicated; **AND**

iv. Medication will **NOT** be used in combination with maintenance immunoglobulin therapy or IV efgartigimod.

II. Efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo) 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. Myasthenia Gravis at dosing frequencies more often than 50 days before the next initial dose
D. Pediatric Myasthenia Gravis
E. Postural Orthostatic Tachycardia Syndrome
F. Primary Immune Thrombocytopenia
G. Atypical Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
H. Bullous Pemphigoid (BALLAD) or Pemphigus (Vulgaris or Foliaceus)

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 a previous prior authorization on efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo) intravenously through a medical approval and is transitioning to subcutaneous; **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., an improvement in the MG-ADL score, improvement/stability in CIDP disease activity status (CDAS) score, improvement in INCAT score, improvement in grip strength, a reduction/elimination of oral steroids/immunosuppressants required, etc); **AND**
IV. Medication will **NOT** be used in combination with maintenance therapies (i.e., immunoglobulin therapy (IVIG), eculizumab (Soliris), ravulizumab (Ultomiris), or rituximab).

Supporting Evidence

I. Efgartigimod alfa (Vyvgart) is FDA approved for the use of adult patients with generalized myasthenia gravis (gMG) that is anti-acetylcholine receptor antibody positive (AChR-AB+) and chronic inflammatory demyelinating polyneuropathy (CIDP). Use in those under the age of 18 has not yet shown safety and efficacy, as well as use in other antibody positive patients.
II. Due to the complexity of diagnosis and treatment, a specialist provider, or consultation with a specialist (e.g., neurologist, rheumatologist) is required.
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 the patient's IgG immune response. This causes common symptoms such as drooping eyelids (ptosis), double vision (diplopia), muscle weakness and fatigue, trouble swallowing or pronouncing words, and facial muscle involvement causing a mask-like appearance or sneer.
IV. Acetylcholine receptors 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 only 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. MG patients are 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 patients 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. Quantitative Myasthenia Gravis 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 patients and a two-point change for a milder patient; 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 not a 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 it should be considered early in the disease over those under 50 with generalized MG or those who fail to respond to an adequate trial of immunotherapy. The only biologic currently included in these same guidelines is eculizumab (Soliris) which is recommended in the treatment of severe, refractory, AChR-AB+ generalized MG. Refractory disease is defined by Internal consensus guidelines, as MG-ADL/QMG unchanged or worse after corticosteroids and a least two other immunosuppressant agents, used in adequate doses for an adequate duration (usually 12 weeks), with persistent symptoms or side effects that limit functioning.

VIII. Pyridostigmine should be the initial therapy in the treatment of patients with gMG and patients should remain on this, unless there is an intolerance to it, throughout the lifetime of the patient's disease. The ability to discontinue pyridostigmine can be an indicator that the patient has met therapy goals and may lead to tapering of other therapies. Next line agents, which are considered for patients still having bothersome symptoms, are nonsteroidal immunosuppressants (NISTs), those that can be used in MG include 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, 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, to return to clinical baseline.

IX. The safety and efficacy of efgartigimod alfa (Vyvgart) intravenously (IV) was studied in a 26-week, Phase 3, randomized, double-blind, placebo-controlled, global trial (ADAPT). One hundred and sixty-seven adult patients with generalized myasthenia gravis staged between II and IV, and had a MG-ADL score of at least 5 with 50% of that score not being from ocular assessment. Patients were randomized 1:1 to receive efgartigimod alfa (n=84, Vyvgart) 10mg/kg or placebo (n=83) as four weekly infusions per one cycle. Patients could remain on standard of care therapies at stable doses; plasmapheresis and IVIG were not allowed during the study. The majority of patients were AChR-AB+, 65 in the treatment arm and 64 in the placebo arm. The primary endpoint was the number of responders in AChR-AB+ patients on the MG-ADL score at week four in efgartigimod alfa (Vyvgart) versus placebo. A responder was defined as a patient who had a two-point or greater reduction in the MG-ADL maintained for four consecutive weeks after the last infusion of the cycle.

X. A statistically significant difference favoring efgartigimod alfa (Vyvgart) over placebo in AChR-AB+ patients was seen at the end of the first treatment cycle. Forty-four of 68 patients in the treatment arm and 19 of 64 patients in the placebo arm experienced a response, OR 4.95 (95CI: 2.21, 11.53; *p<0.0001*). Secondary endpoints looked at response in QMG in AChR-AB+ patients at end of cycle one, MG-ADL response in all patients at the end of cycle one. Endpoints are shown in the following table:

Primary Endpoint	**Efgartigimod alfa (n= 65)***	**Placebo (n=64)***	**Odds Ratio (95% CI); *p* value**
MG-ADL responder in cycle 1 (n, %)	44 (68)	19 (30)	4.95 (2.21-11.53); *p <0.0001*
Secondary Endpoints	**Efgartigimod alfa**	**Placebo**	**Odds Ratio (95% CI); *p* value**
Quantitative Myasthenia Gravis (QMG) responder in cycle one (n,%)	41 (63)*	9 (14)*	10.84 (4.18-31.20); *p<0.0001*
MG-ADL responder in cycle 1 (n,%)	57 (68)$^{\pm}$	31 (37)$^{\pm}$	3.70 (1.85-7.58); *p<0.0001*

**AChR-AB+ patients; ±All study patients, Efgartigimod alfa (n=84), placebo (n=83)*

XI. Patients could continue to repeat cycles of either efgartigimod alfa (Vyvgart) or placebo during the 26-week trial as long as they had a minimum eight-week period between the first doses of each cycle, had an MG-ADL score of at least 5 with 50% due to non-ocular symptoms, and the patient had a sustained two-point improvement for at least four weeks post last cycle dose. Patients who required rescue therapy (change in standard of care medications, addition of IVIG/plasmapheresis, added glucocorticoid therapy) were discontinued from the trial. Those that did not maintain a four-week sustained two-point improvement were considered non-responders and discontinued from the trial.

XII. The data for subcutaneous injections (SC) comes from ADAPTsc, a pharmacodynamic noninferiority, Phase 3, open-label study comparing 10mg/kg IV to 1000mg SC. The primary endpoint evaluated the percentage change from baseline in total IgG levels from week 0 to week 4 in both groups; the body's IgG is partially responsible for the autoimmune activity attacking the ACh receptors in the synapse. Those using SC had a decrease of 66.4 and IV had a decrease of 62.2; a least mean squares difference of 4.2 (0.66-7.73 95%CI, *p<0.0001*) confirming noninferiority. Secondary exploratory endpoints showed consistent similar outcomes of the SC vs. IV for MG-ADL, QMG during one treatment cycle.

XIII. Patients who completed ADAPT without losing response to efgartigimod alfa (Vyvgart) could enroll in a three-year open-label extension (OLE; ADAPT+, N=151) tracking safety, tolerability, and efficacy. To date, the incidence of adverse events (AEs) is similar to ADAPT and efgartigimod alfa (Vyvgart) treatment has shown repeatable and consistent decreases in MG-ADL and QMG scores over multiple cycles. There has been one patient receiving 13 cycles with the majority receiving eight cycles and an average cycle duration of 55 days without additional adverse events with longer-term use.

XIV. A reach out to an expert in the field of neurology indicated that efgartigimod alfa (Vyvgart) has been being used as rescue therapy in patients not controlled on conventional therapy (e.g., pyridostigmine, NISTs). If the patient is asymptomatic (MG-ADL less than 5) on SOC medication it is unlikely they would qualify for efgartigimod alfa (Vyvgart). Therefore if a patient improved on efgaritigmod alfa (Vyvgart) over a one-year period, there could potentially be a titration off of standard of care (SOC) medications, first with oral steroids, or a NIST later in the course of the disease, noting disease progression is worse than the AE of SOC medications or efgartigimod alfa (Vyvgart).

XV. There are currently four other biologics approved in the treatment of MG: eculizumab (Soliris), raculizumab (Ultomiris), zilucoplan (Zilbrysq), and rozanolixizumab (Rystiggo). Soliris is included in the latest guidelines, the Internal Consensus Guidelines on Myasthenia Gravis 2020, in refractory MG with a recommendation after failure of IVIG, plasmapheresis, and immunosuppressive agents. The exclusion criteria for three of these trials, eculizumab (Soliris), raculizumab (Ultomiris), and efgartigimod alfa (Vyvgart), 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 experimental.

XVI. The minimum time to the initiation of another treatment cycle in ADAPT was 56 days; however, ADAPT+ defined its protocol to allow the minimum time to another treatment cycle of 50 days. Doses sooner than 50 days between the initial dose of each cycle have not been assessed for safety or efficacy and would be experimental in use.

XVII. Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated neuropathy that primarily affects peripheral nerves, and nerve roots and commonly presents with a relapsing-remitting or progressive course. Over time, symmetric weakness of muscles can exceed the extent of sensory loss, is the most common type affecting 50 to 60% of all cases and considered 'typical' CIDP. Disease not characterized by symmetrical weakness is considered atypical CIDP.

XVIII. The European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) recommends induction and maintenance therapy with first-line treatment such as corticosteroids, IVIG and plasma exchange. Subcutaneous immune globulin (SCIG) can also be considered for maintenance treatment. The guidelines do not report one therapy over another and consideration of treatment should be assessed based on patient disease factors and treatment tolerability. In a disease with no cure, the goal of therapy for CIDP is to stop the immune attach against the myelin sheath of peripheral nerves to minimize axonal degeneration and improve symptom control and function.

XIX. Efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo) was studied in a Phase 2, randomized-withdrawal, double-blind, multicentered trial (ADHERE) that enrolled a total of 322 participants. The study was done in two stages: stage A participants (n=322) received 1000mg weekly of efgartigimod PH20 subcutaneous injection for 12 weeks and stage B participants (n=221) were randomized (1:1) to receive either continuing efgartigimod PH20 therapy weekly or matched placebo for 48 weeks. Baseline characteristics included a median age of 54 years, predominantly male (65%), and a diagnosis of typical CIDP (85%). Treatment-experienced patients were required to discontinue their current standard-of-care therapies during the study.

XX. The results of stage A had 66% of participants have a confirmed clinical improvement on therapy based on an improvement of INCAT by at least ≥1 point or ≥4 points on I-RODS or ≥8kPa on grip strength. In stage B, there was a risk reduction rate of 61% between the treatment group and placebo (HR 0.39; 95% CI 0.253, 0.614; p<0.0001). There was a total of 31 participants in the treatment group that experienced a relapse as compared to 59 participants in the placebo group (ARR: 25%) which is comparable to immunoglobulin therapy.

XXI. About 63-64% of patients reported an adverse event (AE) who received efgartigimod alfa and hyaluronidase (Vyvgart Hytrulo) as compared to 56% in the placebo group. The most common AE reported in the treatment group was injection site erythema (10%), CIDP worsening (5%), and headaches (5%) in stage A. In stage B, common AEs reported include COVID-19 (17% vs.

13%) and inject site reactions (14% vs. 6%). There was a total of 3 reported deaths all deemed not related to the study drug.

Investigational or Not Medically Necessary Uses

I. Efgartigimod alfa (Vyvgart) 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. Myasthenia Gravis at dosing frequencies more often than 50 days before the next initial dose
   D. Pediatric Myasthenia Gravis
   E. Postural Orthostatic Tachycardia Syndrome
   F. Primary Immune Thrombocytopenia
   G. Atypical chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
   H. Bullous Pemphigoid (BALLAD) or Pemphigus (Vulgaris or Foliaceus)

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. Vyvgart Hytrulo. Prescribing Information. Argenx BV; December 2021. Revised April 2025.
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. doi: 10.1212/WNL.0000000000011124. Epub 2020 Nov 3.
3. Howard JF Jr, Bril V, Vu T, et al; ADAPT Investigator Study Group. Poster #108: Long-Term Safety, Tolerability, and Efficacy of Efgartigimod in patient with Generalized Myasthenia Gravis: Interim Results of the ADAPT+ Study. Presented at the American Association of Neuromuscular and Electrodiagnostic Medicine Annual Meeting: September 21-24; Nashville, TN, USA
4. Howard JF Jr, Bril V, Vu T, et al; ADAPT Investigator Study Group. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2021 Jul;20(7):526-536. doi: 10.1016/S1474-4422(21)00159-9. Erratum in: Lancet Neurol. 2021 Aug;20(8):e5.
5. Mantegazza, Renato, Li, George, Margania, Temur, et. al. ADAPTsc: a phase 3, randomized, open-label, parallel-group, noninferiority study comparing subcutaneous injections of efgartigimod PH20 1000mg with intravenous infusions of efgartigimod 10mg/kg. Poster #312, presented at the 7th Internal Myology Congress, September 12-15, 2022; Nice, France
6. Heo YA. Efgartigimod: First Approval. Drugs. 2022 Feb;82(3):341-348. doi: 10.1007/s40265-022-01678-3. Erratum in: Drugs. 2022 Apr;82(5):611.
7. Allen JA, Lin J, Basta I, et al. Safety, tolerability, and efficacy of subcutaneous efgartigimod in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ADHERE): a multicentre, randomised-withdrawal, double-blind, placebo-controlled, phase 2 trial [published correction appears in Lancet Neurol. 2025 May;24(5):e8. doi: 10.1016/S1474-4422(25)00108-5.]. Lancet Neurol. 2024;23(10):1013-1024. doi:10.1016/S1474-4422(24)00309-0
8. Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision [published correction appears in Eur J Neurol. 2022 Apr;29(4):1288. doi: 10.1111/ene.15225.]. *Eur J Neurol*. 2021;28(11):3556-3583. doi:10.1111/ene.14959

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
zilucoplan (Zilbrysq®)	Myasthenia Gravis

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	08/2025

eflornithine (Iwilfin™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP302

Description

Eflornithine (Iwilfin) is an ornithine decarboxylase inhibitor.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months*; maximum total (lifetime) fills should not exceed #24 30-day fills

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
eflornithine (Iwilfin)	High-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy	192 mg tablets	See appendix*

**Please note that the dose is based on body surface area (BSA). Please see appendix for dosing limits.*

Initial Evaluation

I. **Eflornithine (Iwilfin)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. Medication will not be used in combination with any other oncology therapy; **AND**
   C. A diagnosis of **high-risk neuroblastoma (HRNB)** when the following are met:
      1. Provider attestation that the member has high-risk disease as defined by International Neuroblastoma Risk Group Classification criteria; **AND**
      2. Documentation of member's weight and height within the last three months; **OR**
         i. Documentation of the member's body surface area (BSA) within the last three months; **AND**
      3. The member has undergone prior therapy with induction therapy (e.g. cisplatin, etoposide, vincristine, cyclophosphamide, doxorubicin, topotecan, surgical resection); **AND**
      4. The member has been previously treated with consolidation therapy [e.g., myeloablative chemotherapy (carboplatin, etoposide, melphalan or busulfan, melphalan) and HSCT]; **AND**
      5. The member has been previously treated with post consolidation therapy consisting of all of the following unless contraindicated, or not tolerated:
         i. Isotretinoin
         ii. Granulocyte-macrophage colony-stimulating factor (e.g., sargramostim)
         iii. Anti-GD2 immunotherapy (e.g., dinutuximab)

II. Eflornithine (Iwilfin) is considered not medically necessary when criteria above are not met and/or when used for:

A. Reduction of unwanted facial hair

III. Eflornithine (Iwilfin) is considered investigational when used for all other conditions, including but not limited to:
   A. Eflornithine (Iwilfin) used in combination with another oncology therapy
   B. Low-risk neuroblastoma
   C. Intermediate risk neuroblastoma
   D. West African trypanosomiasis

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 stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Documentation of member's weight and height within the last three months; **OR**
   A. Documentation of the member's body surface area (BSA) within the last three months; **AND**
V. The member has not received treatment with eflornithine (Iwilfin) for more than 24 months

Supporting Evidence

I. Eflornithine (Iwilfin) is an ornithine decarboxylase inhibitor FDA approved to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.
II. Neuroblastomas are the most common extracranial solid tumor in childhood. They can arise anywhere throughout the sympathetic nervous system though the adrenal gland is the most common primary site (40%). Symptoms at presentation vary based on the site of primary disease, the most common symptoms include abdominal masses, bone pain and pancytopenia from bone marrow metastasis, and proptosis and periorbital ecchymosis due to retrobulbar metastases.
III. Outcomes for patients with HRNB remain poor despite treatment with multiple treatment modalities. Treatment for patients is generally divided into three steps including induction (chemotherapy and surgery), consolidation (tandem cycles of myeloablative therapy and HSCT and radiation therapy to the site of the primary tumor and residual metastatic sites), and post consolidation [immunotherapy with granulocyte-macrophage colony-stimulating factor (GM-CSF), dinutuximab, and isotretinoin therapy). However, after post consolidation treatment options are limited. Eflornithine (Iwilfin) is the first FDA approved maintenance therapy for those with HRNB after multimodal therapy (i.e., induction, consolidation, post consolidation including anti-GD2s).
IV. The diagnosis of neuroblastoma requires the involvement of pathologists who are familiar with childhood tumors. Some neuroblastomas cannot be differentiated morphologically, via conventional light microscopy. Given the complexities related to diagnosis, treatment, and

management of HRNB, treatment in this disease space must be initiated by, or in consultation with, an oncologist.

V. Eflornithine (Iwilfin) is an orally administered tablet given twice per day based on body surface area. Per the FDA label it is recommended to recalculate the BSA every three months. Therefore, this policy asks for the member's height and weight within the past three months in order to calculate an appropriate dose.

VI. Eflornithine (Iwilfin) was studied in a Phase 2, multi-center, open label, non-randomized trial (Study 3b). Study 3b was prospectively designed to compare outcomes to the historical benchmark event free survival (EFS) rate from Study ANBL0032 (clinical trial-derived external control arm). The external control arm was derived from 1,241 patients on the experimental arm of Study ANBL0032, a Phase 3, multi-center, open-label, randomized trial of dinutuximab, GM-CSF, interleukin-2, and cis-retinoic acid compared to cis-retinoic acid alone in pediatric patients with HRNB.

VII. Patients eligible for Study 3b had a histologically confirmed diagnosis of neuroblastoma with high-risk disease according to the International Neuroblastoma Risk Group Classification. Patients are stratified by several factors that define the risk of relapse, including age, disease stage, and other tumor attributes. Based on these factors, patients are diagnosed with low-, intermediate- or high-risk disease. Current neuroblastoma high-risk stratification criteria include:

- Stage 2A or 2B disease and MYCN amplification
- Stage 3 disease and MYCN amplification
- Stage 3 disease in children aged ≥ 18 months, no MYCN amplification and unfavorable histopathology
- Stage 4 disease in children younger than 12 months and with MYCN amplification
- Stage 4 disease in children aged 12–18 months with MYCN amplification and/or diploidy and/or unfavorable histology
- Stage 4 disease in children aged ≥ 18 months
- Stage 4S disease and MYCN amplification

VIII. Trial participants had received upfront therapy defined as chemotherapy (5-7 cycles), surgery as indicated, consolidation therapy as indicated, radiation therapy as indicated, anti-GD2 antibody therapy with retinoic acid up to 6 cycles.

- While induction chemotherapies are not standardized across institutions, the most common backbone of therapy includes dose-intensive cycles of cisplatin and etoposide alternating with vincristine, cyclophosphamide, and doxorubicin. Topotecan and cyclophosphamide were added to this regimen on the basis of the anti-neuroblastoma activity seen in patients with relapsed disease. After a response to induction chemotherapy, resection of the primary tumor is usually attempted. The consolidation phase of high-risk regimens involves myeloablative chemotherapy and HSCT, which attempts to eradicate minimal residual disease (MRD) using otherwise lethal doses of ablative chemotherapy rescued by autologous stem cells (collected during induction chemotherapy) to repopulate the bone marrow. Most current protocols use tandem chemotherapy and HSCT with carboplatin/etoposide/melphalan or busulfan/melphalan as conditioning for HSCT. Post consolidation therapy is designed to treat potential MRD after HSCT. For high-risk patients in remission after HSCT, dinutuximab combined with GM-CSF given together with isotretinoin demonstrated improved EFS as demonstrated in study

ANBL0032. The end of study ANBL0032 represented the end of immunotherapy and served as the baseline for Study 3b.

IX. Patients who met the criteria for the comparative analysis of Study 3b and ANBL0032, with complete data for specified clinical covariates (age at high-risk diagnosis, sex, race, stage at HRNB, pre-ASCT response, transplant type, time from ASCT to start of immunotherapy, duration of immunotherapy, overall response at immunotherapy end, time from diagnosis to immunotherapy end, and MYCN category), were matched (1:3) using propensity scores. The efficacy populations for the primary analysis included 90 patients treated with eflornithine (Iwilfin) and 270 control patients from Study ANBL0032.

X. Four-year EFS and OS outcomes were reported in two populations, the propensity score matched (PSM) the group and the overall population. In the PSM population a four-year EFS of 84% was reported in the (Iwilfin) compared to 73% in the external control arm for a treatment difference of 0.48 (95% CI, 0.27 to 0.85; P=.01). The four-year OS was found to be 96% in the eflornithine (Iwilfin) treated group compared to 84% in the external control arm for a treatment difference of 0.32 (95% CI, 0.15 to 0.70; P=.005). Similar results were reported in the overall population with a four-year EFS of 84% vs 72% respectively [HR 0.50 (95% CI, 0.29 to 0.84; P= .008)] and a four-year OS of 96% vs 84% [HR 0.38 (95% CI, 0.19 to 0.76; P=.007)].

XI. Most adverse effects (AE) were mild to moderate in severity. In a pooled safety population, the most common adverse reactions were hearing loss (11%), otitis media (10%), pyrexia (7%), pneumonia (5%), and diarrhea (5%). There are no specific contraindications to the use of eflornithine (Iwilfin).

XII. The use of eflornithine (Iwilfin) has not been studied in combination with other oncolytic therapies. Due to a lack of safety and efficacy data with a combination regimen eflornithine (Iwilfin) is to be used as monotherapy.

Investigational or Not Medically Necessary Uses

I. Reduction of unwanted facial
   A. Treatment with eflornithine (Iwilfin) for the reduction of unwanted hair falls in the category of medications that are not covered under the prescription benefit. Drugs used for cosmetic purposes are excluded from coverage.

II. Eflornithine (Iwilfin) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Eflornithine (Iwilfin) used in combination with another oncology therapy
   B. Low-risk neuroblastoma
   C. Intermediate risk neuroblastoma
   D. West African trypanosomiasis
      i. Injectable eflornithine is donated to the World Health Organization (WHO) by the manufacturer. In the United States, eflornithine injection is available through the CDC for treatment of second-stage African trypanosomiasis (caused by Trypanosoma brucei gambiense) with CNS involvement.

Appendix

I. Table 1: Recommended Dose

Body Surface Area (m^2)	Dosage
>1.5	768 mg (four tablets) orally twice a day

0.75 to 1.5	576 mg (three tablets) orally twice a day
0.5 to < 0.75	384 mg (two tablets) orally twice a day
0.25 to <0.5	192 mg (one tablet) orally twice a day

References

1. Iwilfin. Package Insert. USWorldMeds; December 2023.
2. Oesterheld J, Ferguson W, Kraveka JM, et al. Eflornithine as Postimmunotherapy Maintenance in High-Risk Neuroblastoma: Externally Controlled, Propensity Score-Matched Survival Outcome Comparisons. *J Clin Oncol*. 2024;42(1):90-102.
3. Sholler GLS, Ferguson W, Bergendahl G, et al. Maintenance DFMO Increases Survival in High Risk Neuroblastoma. *Sci Rep*. 2018;8(1):14445. Published 2018 Sep 27.
4. PDQ® Pediatric Treatment Editorial Board. PDQ Neuroblastoma Treatment. Bethesda, MD: National Cancer Institute. Updated 12/22/2023. Available at: https://www.cancer.gov/types/neuroblastoma/hp/neuroblastoma-treatment-pdq. Accessed 01/18/2024. [PMID: 26389190]
5. National Comprehensive Cancer Network. Neuroblastoma (Version 1.2024). NCCN. February 7, 2024. Accessed March 19, 2024. https://www.nccn.org/professionals/physician_gls/pdf/neuroblastoma.pdf

Related Policies

The 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
ALK+ Inhibitors Policy	ALK+ metastatic NSCLC
	ROS1+ metastatic NSCLC
	ALK+ R/R inflammatory myofibroblastic tumors

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2024

elacestrant (Orserdu™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP275

Description

Elacestrant (Orserdu) is an orally administered estrogen receptor antagonist indicated for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer.

Length of Authorization

- Initial: 6 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
Elacestrant (Orserdu)	Breast cancer, HER2-negative, HR-positive, ESR1-positive advanced or metastatic	345 mg tablet	30 tablets/30 days
		86 mg tablet	90 tablets/30 days*

**Quantity Limit Exceptions are not allowed*

Initial Evaluation

I. **Elacestrant (Orserdu)** 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. Medication will not be used in combination with any other oncolytic therapy; **AND**
   D. The member is a postmenopausal female, premenopausal or perimenopausal female receiving ovarian suppression/ablation (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **OR**
      1. The member is hormone suppressed male (e.g., GnRH therapy [e.g., leuprolide] used concomitantly); **AND**
   E. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. The breast cancer is HR-positive, and HER2-negative; **AND**
      2. Documentation that the member has ESR1 mutation as confirmed by an FDA approved test (e.g., Guardant360 CDx assay); **AND**
      3. The member had disease progression on, or after treatment with a CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.); **AND**
      4. The member has had disease progression on at least one prior endocrine therapy for advanced or metastatic breast cancer (e.g., fulvestrant, letrozole, anastrozole, exemestane, tamoxifen)

II. Elacestrant (Orserdu) is considered investigational when used for all other conditions, including but not limited to:

A. Elacestrant (Orserdu) used in combination with another oncolytic therapy
B. Breast cancer that is not HR+, HER2-, ESR1 mutated
C. Neoadjuvant or adjuvant therapy for early-stage non-metastatic breast cancer (i.e., not advanced or metastatic)

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 will not be used in combination with any other oncolytic therapy; **AND**
IV. Member has exhibited response to the treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Elacestrant (Orserdu) is the first medication FDA-approved specifically targeting ESR1 mutation. It joins many other agents for the treatment of ER/PR-positive, HER2-negative, advanced, or metastatic breast cancer. Elacestrant (Orserdu) is FDA-approved for the treatment of patients 18 years of age and older. Safety and efficacy of elacestrant (Orserdu) has not been studied in the pediatric population. Additionally, the current clinical data only supports the use of elacestrant (Orserdu) as a monotherapy.
II. The recommended dosage of elacestrant (Orserdu) is 345 mg taken orally with food once daily until disease progression or unacceptable toxicity occurs. Elacestrant (Orserdu) is also available as an 86 mg formulation, which is only utilized when dose reductions are necessary due to drug toxicity.
III. Given the complexities involved with the diagnosis and treatment of breast cancer, systemic therapy for advanced or metastatic breast cancer must be initiated and supervised by an oncologist.
IV. Endocrine therapy (ET), specifically an aromatase inhibitor (AI; e.g., anastrozole, letrozole, or exemestane) or fulvestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (e.g., ribociclib, abemaciclib) is the preferred first-line treatment for ER-positive, HER2-negative, metastatic breast cancer. After disease progression, options depend on the type of previous therapy received. These include endocrine monotherapy with fulvestrant, an AI, or tamoxifen, everolimus plus ET, alpelisib in combination with fulvestrant (PIK3CA mutated only), and chemotherapy. Sequential ET is preferred over chemotherapy due to toxicity. Presence of an ESR1 mutation limits sequential ET options as these tumors are typically resistant to both AIs and tamoxifen. However, certain tumors with ESR1 mutation may retain sensitivity to fulvestrant.
V. The expected place in therapy for elacestrant (Orserdu) is in the second- or third-line setting, after progression on or after endocrine therapy (first or second line), including one line containing a CDK4/6 inhibitor in patients with ESR1 mutation. National Comprehensive Cancer Network guidelines for the treatment of breast cancer have been updated to include elacestrant

(Orserdu) in other recommended regimens as the subsequent-line therapy for ESR1 mutated recurrent, advanced, or metastatic (stage IV) disease (Category 2A recommendation).

VI. Elacestrant (Orserdu) was studied in a Phase III, randomized, open-label, multicenter trial (EMERALD) against standard of care (SOC) ET, which included fulvestrant or AIs. The clinical trial participants (N= 478) included postmenopausal women and men with ER-positive, HER2-negative advanced or metastatic breast cancer. The median age was 63 years, 228 patients (47.8%) had ESR1 mutation (all female), all had prior CDK4/6 inhibitor therapy (100%), 207 (43.4%) received two prior lines of ET, and 106 (22.2%) received one prior chemotherapy. The primary and secondary outcomes were evaluated in all patients and in those with ESR1 mutation and included progression-free survival (PFS) and overall survival (OS), respectively.

VII. Elacestrant (Orserdu) reported a statistically significant improvement in PFS compared to SOC in patients with ESR1 mutation (median PFS 3.8 months vs 1.9 months, p=0.0005). Although median OS did not reach statistical significance in the ESR1 mutated subpopulation, OS numerically favored the elacestrant (Orserdu) arm (24.2 months vs 23.5 months). The PFS endpoint was also met in the intention to treat population, however, the US FDA considered these results to be driven by the 48% of patients in the ESR1 mutated subpopulation. In an exploratory analysis of ESR1 non-mutated population, the median PFS was 1.9 months for elacestrant (Orserdu) and 2.0 months for SOC (HR 0.86, 95% CI: 0.63-1.19).

V. The safety profile of elacestrant (Orserdu) is similar or slightly less favorable when compared to SOC endocrine therapy. Most common adverse events (AE) for elacestrant (Orserdu) versus SOC, respectively, were musculoskeletal pain (41% vs 39%) nausea (35% vs 18.8%), fatigue (19.0% vs 18.8%), vomiting (19.0% vs 8.3%), decreased appetite (14.8% vs 9.2%), arthralgia (14.3% vs 16.2), cholesterol increase (30% vs 17%), and triglycerides increase (27% vs 15%). Treatment-related grade 3/4 AEs and events leading to discontinuation for elacestrant (Orserdu) versus standard of care therapies were 7.2% versus 3.0% and 3.4% versus 0.9%, respectively. The most common grade 3/4 adverse events for elacestrant (Orserdu) were musculoskeletal pain (7%) and nausea (2.5%).

VI. NCCN panel recommends that patients with HR-positive disease should have adequate ovarian suppression/ablation and that these patients be treated in the same way as post-menopausal patients. Within the EMERALD trial, patients receiving ovarian ablation were included, but patients receiving ongoing hormone suppression were excluded. However, current practice consensus and historical clinical data in advanced breast cancer therapy supports the use of systemic therapies in all female patients, including premenopausal or perimenopausal females, provided these patients achieve a hormone-induced (GnRH analog such as leuprolide (Lupron)) or surgery-induced menopause. It is expected that the response to oncolytic therapies in these patient populations may be clinically comparable to that in naturally postmenopausal patients.

Investigational or Not Medically Necessary Uses

I. Elacestrant (Orserdu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Elacestrant (Orserdu) used in combination with another oncolytic therapy
   B. Breast cancer that is not HR+, HER2-, ESR1 mutated
   C. Neoadjuvant or adjuvant therapy for early-stage non-metastatic breast cancer (i.e., not advanced or metastatic)

References

1. Orserdu [Prescribing Information]. Stemline Therapeutics, Inc.; January 2023.
2. National Comprehensive Cancer Network. Breast Cancer. NCCN. March 3, 2023. Accessed March 4, 2023. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
3. Bidard FC, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) Versus Standard Endocrine Therapy for Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Randomized Phase III EMERALD Trial. *J Clin Oncol*. 2022;40(28):3246-3256. doi:10.1200/JCO.22.00338
4. Breast Cancer – Metastatic: Statistics. Cancer.net. February 2023. Accessed March 7, 2023. https://www.cancer.net/cancer-types/breast-cancer-metastatic/statistics
5. Brett, J.O., Spring, L.M., Bardia, A. *et al.* ESR1 mutation as an emerging clinical biomarker in metastatic hormone receptor-positive breast cancer. *Breast Cancer Res* 23, 85 (2021). https://doi.org/10.1186/s13058-021-01462-3
6. Ahn, S.G., Bae, S.J., Kim, Y. *et al.* Primary endocrine resistance of ER+ breast cancer with *ESR1* mutations interrogated by droplet digital PCR. *npj Breast Cancer* 8, 58 (2022). https://doi.org/10.1038/s41523-022-00424-y

Related Policies:

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2023

eluxadoline (Viberzi®)

UMP POLICY

Policy Type: PA Pharmacy Coverage Policy: UMP179

Description

Eluxadoline (Viberzi) is an orally administered mu-opioid receptor agonist that interacts with receptors in the stomach.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
eluxadoline (Viberzi)	75 mg tablets	Irritable bowel syndrome with diarrhea (IBS-D)	60 tablets/30 days
	100 mg tablets		

Initial Evaluation

I. Eluxadoline (Viberzi) may be considered medically necessary when the following criteria are met:
   A. A diagnosis of **Irritable Bowel Syndrome with Diarrhea (IBS-D)**; **AND**
      1. The member is 18 year of age or older; **AND**
      2. Prescribed by, or in consultation with, a gastroenterologist; **AND**
      3. Treatment with at least three therapies from three different groups have been ineffective, not tolerated, or **ALL** are contraindicated (please note, if one or more groups is contraindicated, a trial of three agents from the remaining groups will be required):
         a. Group 1: antidiarrheal (e.g. loperamide, bismuth subsalicylate, diphenoxylate/atropine, or paregoric)
         b. Group 2: bile acid sequestrant (e.g. cholestyramine and colestipol)
         c. Group 3: antispasmodic (e.g. dicyclomine and hyoscyamine)
         d. Group 4: Tricyclic serotonergic agent: (e.g. amitriptyline, nortriptyline, imipramine, or desipramine)

II. Eluxadoline (Viberzi) is considered investigational when used for all other conditions, including but not limited to:
   A. Diabetic diarrhea
   B. Diarrhea associated with fecal incontinence
   C. Pediatric IBS-D
   D. Mixed IBS or IBS with constipation

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
IV. The member has demonstrated a beneficial response to therapy [e.g., symptomatic improvement, improvement in pain associated with IBS-D, a decrease in score for the Bristol Stool Scale (BSS) for stool consistency]

Supporting Evidence

I. The efficacy and safety of eluxadoline (Viberzi) for IBS-D was evaluated in two randomized, double-blind, placebo-controlled trials. Treatment arms were 75 mg, 100 mg or placebo, all administered twice daily. Patients were 18-80 years of age, and all met ROME III criteria for IBS-D. Patients, on average, had a pain score of 3 (0-10) in abdominal pain due to IBS-D, an average daily stool consistency of 5.5 or greater, and at least five days with a BSS score of 5 or greater (1-7). The BSS for stool consistency is rated on a scale of 1-7, with 1 being hard to pass or lumpy stool, and 7 being entirely liquid stool. Efficacy was assessed via a responder composite endpoint of simultaneous improvement in the daily worse abdominal pain score by 30% or greater compared to baseline AND a reduction in BSS to less than 5 for at least half of the days within a 12-week timeframe.
    - Study 1: A 26-week study of 1281 patients, with an additional 26 weeks for safety evaluation. Eluxadoline (Viberzi) showed a 23-29% response rate compared to 17% for placebo. Composite response rates were statistically significant at 12 weeks for both strengths, and the 26-week endpoint was statistically significant for the 100 mg.
    - Study 2: A 26-week study of 1145 patients. This study also included a 4-week withdrawal period upon completion of the 26-week phase. During the withdrawal period, patients were permitted to take rescue loperamide therapy for uncontrolled diarrhea. Eluxadoline (Viberzi) showed a 29-33% response rate compared to 16-20% for placebo. Composite response rates were statistically significant for both strengths at week 12 and 26.
II. Conventional treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants; all of which, the American College of Gastroenterology gave moderate or weak recommendations because of poor quality of evidence and applicability to patient groups. However, due to insufficient comparative evidence for efficacy, conventional treatment options still provide a better value over eluxadoline (Viberzi). Notably, Of the antidepressants, tricyclic agents have been shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.

Investigational or Not Medically Necessary Uses

I. Eluxadoline (Viberzi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Diabetic diarrhea
   B. Diarrhea associated with fecal incontinence
   C. Pediatric IBS-D
   D. Mixed IBS or IBS with constipation

References

1. Viberzi [Prescribing Information]. Madison, NJ: Allergan USA. April 2018.
2. U.S. National Library of Medicine. clinicaltrials.gov. https://clinicaltrials.gov/ct2/results?cond=eluxadoline&term=&cntry=&state=&city=&dist=. Accessed March 2020.
3. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for Irritable Bowel Syndrome with Diarrhea. N Engl J Med. 2016;374(3):242-53.
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. http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/. Accessed March 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Update to three conventional therapies required prior to coverage. Update to require specialist prescriber.	04/2020
Policy Created	02/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP091

Description

Encorafenib (Braftovi) is a kinase inhibitor of in-vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. Binimetinib (Mektovi) is a reversible kinase inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity. These agents are FDA-approved for combination use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
encorafenib (Braftovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy; Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy Metastatic non-small cell lung cancer, with BRAF V600E mutation, combination therapy	50 mg capsule	180 capsules/30 days
		75 mg capsule	180 capsules/30 days
binimetinib (Mektovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy Metastatic non-small cell lung cancer, with BRAF V600E mutation, combination therapy	15 mg tablet	180 tablets/30 days

Initial Evaluation

I. **Encorafenib (Braftovi) and binimetinib (Mektovi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Encorafenib (Braftovi) and binimetinib (Mektovi) will **not** be used in combination with any other oncolytic agent unless specified below (e.g. encorafenib (Braftovi) and cetuximab (Erbitux) for the treatment of colorectal cancer); **AND**
   C. The member has **not** progressed on prior BRAF-inhibitor therapy (e.g., dabrafeinib, vemurafenib); **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

D. A diagnosis of one of the following:
    1. **Advanced (stage III) or metastatic (stage IV) cutaneous melanoma**; **AND**
        i. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
        ii. Encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **AND**
        iii. Confirmation of BRAF V600E or V600K; **OR**
    2. **Metastatic (stage IV) colorectal cancer (CRC)**; **AND**
        i. Medication is prescribed by, or in consultation with, an oncologist or gastroenterologist; **AND**
        ii. The request is for encorafenib (Braftovi) in combination with cetuximab (Erbitux); **AND**
        iii. Confirmation of BRAF V600E mutation; **AND**
        iv. The member has previously tried and failed at least one systemic therapy (e.g. FOLFIRI, irinotecan, oxaliplatin)

II. Encorafenib (Braftovi) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Colorectal cancer in combination with binimetinib (Mektovi) and cetuximab (Erbitux)

III. Encorafenib (Braftovi) and binimetinib (Mektovi) are considered investigational when used for all other conditions, including but not limited to:
    A. KRAS-mutated cancer
    B. Adolescents with BRAF-mutant melanoma
    C. Thyroid cancer
    D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
    E. CNS cancers (e.g., glioma, neurofibromas)
    F. Gastrointestinal cancer (e.g., GIST)
    G. Pancreatic cancer
    H. Colorectal cancer in combination with panitumumab (Vectibix)

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; **AND**
III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
    A. For treatment of melanoma: encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **OR**
    B. For treatment of colorectal cancer: encorafenib (Braftovi) and cetuximab (Erbitux) will be used in combination

Supporting Evidence

I. Encorafenib (Braftovi) and binimetinib (Mektovi) are kinase inhibitors FDA approved for use in combination for the treatment of participants with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Encorafenib (Braftovi) in combination with cetuximab (Erbitux) is FDA approved for use in metastatic colorectal cancer (mCRC) with BRAF V600E mutation. Given the complexity of management of metastatic melanoma, and mCRC, treatment must be initiated by, in or consultation with, an oncologist, dermatologist, or gastroenterologist.

II. Advanced or Metastatic Melanoma

- BRAF/MEK inhibitors have been studied in advanced and metastatic melanoma. Surgical resection remains the mainstay of therapy prior to stage III and have favorable outcomes for most patients. Participants at stage II have a high risk of progressing to advanced disease and have a high risk of recurrence; however, there is currently no evidence to support safety and efficacy in this population for any BRAF/MEK therapy combination.
- There is limited evidence regarding the safety and efficacy of BRAF/MEK inhibitor therapy in those that have progressed on a previous or alternative BRAF/MEK therapy combination. Results from a phase I/II study showed that those that had previous BRAF therapy, further treatment with dabrafenib (Tafinlar)/trametinib (Mekinist), had poor response rates, progression free survival (PFS), and overall survival (OS) compared to those that had not been previously treated with these specific mechanisms of action. Most notably, a subset analysis showed that participants who had rapidly progressed on BRAF therapy (less than six months to progression) derived no clinical benefit from second line/subsequent treatment.
- BRAF V600E and V600K mutations are the most common mutation of BRAF driver mutations; however, several other BRAF mutations exist. NCCN supports the use of BRAF/MEK inhibitors for any V600 mutation; however, there is currently no evidence for safety or efficacy to support the use of encorafenib (Braftovi) and binimetinib (Mektovi) in settings outside of V600E or V600K.
- Encorafenib (Braftovi), in combination with binimetinib (Mektovi), was evaluated in a randomized, active-controlled, open-label multicenter trial (n=577). Participants had a BRAF V600E or K mutation-positive, unresectable or metastatic melanoma, and were permitted to have prior immunotherapy for advanced or metastatic disease. Prior use of BRAF therapy was not allowed.
    i. Participants were randomized to receive encorafenib (Braftovi) in combination with binimetinib (Mektovi), encorafenib (Braftovi) monotherapy, or vemurafenib (Zelboraf) monotherapy. The primary outcome was PFS. Secondary outcomes included OS, objective response rate (ORR), and duration of response (DoR).
    ii. The combination of Braftovi and Mektovi showed a statistically significant improvement in PFS compared to vemurafenib (Zelboraf) (14.9 months vs 7.3 months, p<0.0001). There were statistically significant improvements in ORR and DoR. OS data was published in 2018, with OS duration of 33.6 months for combination therapy compared to 16.9 months with vemurafenib monotherapy (p<0.0001).
    iii. The safety and efficacy of combination therapy with Braftovi and Mektovi was evaluated, compared to encorafenib (Braftovi) alone, and results were

more favorable for combination therapy. The current FDA-approval is for dual therapy.

III. Metastatic Colorectal Cancer

- Encorafenib (Braftovi), in combination with cetuximab (Erbitux), was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 participants with BRAF V600E mutation-positive metastatic CRC. The primary efficacy endpoint was OS. The median OS was 9 months for encorafenib (Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 8.4 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 5.4 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.52 (95% CI 0.39, 0.70) and 0.60 (95% CI 0.45, 0.79), respectively. The median PFS was 4.3 months for encorafenib (Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 4.2 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 1.5 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.38 (95% CI 0.29, 0.49) and 0.40 (95% CI 0.31, 0.52), respectively. The estimated six-month survival was 71% in the triple therapy group and 65% in the dual therapy group with a HR of 0.79 (95% CI 0.59, 1.06).
- NCCN guidelines note that triple therapy with encorafenib (Braftovi)/binimetinib (Mektovi)/cetuximab (Erbitux) has evidence for use in metastatic colorectal cancer; however, when listing recommended therapy options, they only note encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix). The recommendation for encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix) is Category 2A. Although both cetuximab (Erbitux) and panitumumab (Vectibix) are listed as combination options within NCCN, clinical data available is limited to encorafenib (Braftovi) in combination with cetuximab (Erbitux).

Investigational or Not Medically Necessary Uses

I. Encorafenib (Braftovi) and binimetinib (Mektovi) have not been sufficiently studied for safety and/or efficacy in the following settings:
   A. KRAS-mutation cancer
   B. Adolescents with BRAF-mutant melanoma
   C. Thyroid cancer
   D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
      i. Encorafenib (Braftovi) and binimetinib (Mektovi) are FDA approved for use in metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation. Encorafenib (Braftovi) and binimetinib (Mektovi) combination therapy was evaluated in a Phase II, open label, multicenter, single arm study. The study included 98 participants, 18 years and older with histologically confirmed stage IV or recurrent NSCLC with BRAF V600E mutation. The cohorts were divided into two groups, those that were treatment naïve and those that had one prior line of platinum-based chemotherapy (those with prior PD-1 inhibitors were included). Baseline median age was 70 years old, 88% of the participants were white, 53% women, and 30% never smoked. The ORR was 75% (95% CI, 62 to 85) in the treatment naïve group and 46% (95% CI, 30 to 63) in those previously treated. Median DOR was not estimable (NE) (95% CI, 23.1 to NE) in treatment naive and 16.7 months (95% CI, 7.4 to NE) in the previously treated group. Disease control

rate (DCR) after 24 weeks was 64% in treatment naive and 41% in previously treated participants. Median PFS was NE (95% CI, 15.7 to NE) in treatment naive and 9.3 months (95% CI, 6.2 to NE) in previously treated participants.

ii. NCCN guidelines recommend encorafenib (Braftovi) and binimetinib (Mektovi) or dabrafenib (Tafinlar) and trametinib (Mekinist) combination therapy as first line treatment for NSCLC with BRAF V600E mutation (category 2A, both preferred). After disease progression, systemic therapy, such as immune checkpoint inhibitors or chemotherapy is recommended. There is no data to support safety and efficacy of sequential BRAF/MEK inhibitor therapy in those that have previously progressed on prior BRAF/MEK inhibitors.

iii. Despite NCCN guideline recommendations, approval of encorafenib (Braftovi) and binimetinib (Mektovi) was based on low quality data (open label, single arm study with a small population). Additionally, there's uncertainty in the clinical meaningfulness of DOR, DCR, and PFS as they are surrogate endpoints which has not been correlated with clinically meaningful outcomes such as morbidity, mortality, HRQoL, functionality, or symptom improvement

E. CNS cancers (e.g., glioma, neurofibromas)

F. Gastrointestinal cancer (e.g., GIST)

G. Pancreatic cancer

H. Colorectal cancer in combination with panitumumab (Vectibix)

i. There have been no large, well-designed studies of encorafenib (Braftovi) or binimetinib (Mektovi) in combination with panitumumab (Vectibix).

I. Encorafenib (Braftovi) in combination with binimetinib (Mektovi) and cetuximab (Erbitux) for colorectal cancer

i. Encorafenib (Braftovi), in combination with binimetinib (Mektovi), and cetuximab (Erbitux) was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 participants with BRAF V600E mutation-positive metastatic colorectal cancer. The efficacy of triple therapy was not significantly superior to dual therapy.

References

1. Dummer R., Ascierto PA., Gogas HJ., et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicenter, open-label, randomized, phase 3 trial. *Lancet Oncol*. 2018. 19(10): 1315-1327.
2. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615.
3. Braftovi (encorafenib) [prescribing information]. Boulder, CO: Array BioPharma Inc; October 2023.
4. Mektovi (binimetinib) [prescribing information]. Boulder, CO: Array BioPharma Inc; October 2023.
5. NCCN Clinical Practice Guidelines in Oncology, Cutaneous Melanoma. V 3.2019. National comprehensive Cancer Network. October 22, 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#melanoma.
6. NCCN Clinical Practice Guidelines in Oncology, Colon Cancer. V 2.2022. National comprehensive Cancer Network. October 27, 2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
7. García-Foncillas J, Sunakawa Y, Aderka D, et al. Distinguishing Features of Cetuximab and Panitumumab in Colorectal Cancer and Other Solid Tumors. Front Oncol. 2019;9:849. Published 2019 Sep 20. doi:10.3389/fonc.2019.00849.
8. Riely GJ, Smit EF, Ahn MJ, et al. Phase II, Open-Label Study of Encorafenib Plus Binimetinib in Patients With BRAFV600-Mutant Metastatic Non-Small-Cell Lung Cancer [published correction appears in J Clin Oncol. 2024 Jan 10;42(2):245]. J Clin Oncol. 2023;41(21):3700-3711.
9. The NCCN Non-Small Lung Cancer Clinical Practice Guidelines in Oncology (Versions 3.2024 – March 12, 2024). 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 26, 2024.

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
trametinib (Mekinist®), dabrafenib (Tafinlar®)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy
	Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy, or monotherapy in 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
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

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria requiring specialist consultation was separated out by indication. Renewal criteria wording was updated to reflect current policies. Updates to E/I section to include encorafenib (Braftovi) and binimetinib (Mektovi) for the treatment of metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation. Added table of related policies.	06/2024
Updates to supportive evidence addressing lack of clinical data available for encorafenib (Braftovi) in combination with panitumumab (Vectibix).	11/2022
Updated with new indication for Braftovi for metastatic colorectal cancer in combination with cetuximab. Updated language to state not for combination use besides agents listed in the criteria. Removed exclusions for colorectal cancer and V600-mutated cancer besides melanoma.	06/2020
Prior authorization criteria transitioned to policy, updated criteria with the following: age edit, allowance of dermatologist prescribing, specialist requirement on renewal.	11/2019
Criteria created	07/2018

ensifentrine (Ohtuvayre™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP306

Description

Ensifentrine (Ohtuvayre) is a nebulized inhibitor of phosphodiesterase (PDE) 3 and PDE4.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
ensifentrine (Ohtuvayre)	Chronic Obstructive Pulmonary Disease (COPD)	3 mg/2.5 mL ampule	150 mL/30 days

Initial Evaluation

I. **Ensifentrine (Ohtuvayre)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A confirmed diagnosis of moderate to severe **Chronic Obstructive Pulmonary Disease (COPD)** when all the following are met:
      1. FEV_1/FVC ratio of < 0.7; **AND**
      2. Post-bronchodilator FEV_1 % predicted of ≥ 30% and ≤ 80%; **AND**
      3. Modified Medical Research Council (mMRC) dyspnea score of ≥ 2; **AND**
   C. Member is currently on triple therapy with a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), and an inhaled corticosteroid [ICS] (e.g., Asmanex); **OR**
   D. Triple therapy with a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), and an inhaled corticosteroid [ICS] (e.g., Asmanex) has been ineffective, not tolerated, or all are contraindicated; **OR**
   E. Eosinophil level is < 100 cells/µL and member is currently on dual therapy with a long-acting beta-2 agonist [LABA] and a long-acting muscarinic antagonist [LAMA] unless ineffective, not tolerated, or all are contraindicated; **AND**
   F. Dual or triple therapy [a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), ± an inhaled corticosteroid [ICS] (e.g., Asmanex)] will be continued in combination with ensifentrine (Ohtuvayre), unless not tolerated or all are contraindicated.

II. Ensifentrine (Ohtuvayre) is considered investigational when used for all other conditions, including but not limited to:
   A. Asthma
   B. Cystic Fibrosis

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

C. Non-Cystic Fibrosis Bronchiectasis

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., improved dyspnea, improved lung function] **AND**
IV. Dual or triple therapy [a long-acting agonist [LABA] (e.g., Striverdi Respimat), a long-acting muscarinic antagonist [LAMA] (e.g., Spiriva Respimat), ± an inhaled corticosteroid [ICS] (e.g., Asmanex)] will be continued in combination with ensifentrine (Ohtuvayre), unless not tolerated or all are contraindicated.

Supporting Evidence

I. Ensifentrine (Ohtuvayre) was studied in multicentered, randomized, double-blind, parallel-group, placebo-controlled duplicative trials, ENHANCE-1 and ENHANCE-2 for 24 weeks. Patients were randomized to receive either ensifentrine (Ohtuvayre) 3mg or placebo. Patients were also allowed to continue their maintenance therapies.
II. The primary efficacy outcome was the average change from baseline forced expiratory volume (FEV1) area under the curve $(AUC)_{0\text{-}12h}$ at week 12. Stratified secondary endpoints include peak FEV1 at week 12, E-RS total score at week 24, SGRQ total score at week 24, and morning trough FEV1 at week 12. The primary outcome was met in both trials with an FEV1 change from baseline of 61mL on ensifentrine (Ohtuvayre) and -26mL on placebo (difference of 87mL [95% CI, 55 to 119; p<0.001]) for ENHANCE-1 and 48mL on ensifentrine (Ohtuvayre) and -46mL on placebo (difference of 94mL [95% CI, 64 to 124; p<0.001]) for ENHANCE-2.
III. The improvement in FEV1 is statistically significant compared to placebo Although it is a modest change from baseline, there were associated improvements in symptoms and exacerbation rates. A pooled data analysis of ENHANCE-1 and ENHANCE-2 completed by the manufacturer and independently verified by the Institute for Clinical and Economic Review (ICER) group saw a 41% reduction in exacerbation rates and a 41% reduction in time to first exacerbation event compared to placebo at week 24. Collectively, there's moderate confidence that ensifentrine (Ohtuvayre) provides a clinically meaningful benefit to patients in the treatment of COPD, providing a similar overall treatment profile to standard of care agents (LAMA/LABA ± ICS).
IV. Nasopharyngitis and upper respiratory tract infections were the most commonly reported adverse events. The pooled incidence rates for nasopharyngitis were 2.6% vs. 0% and for upper respiratory tract infections, 1.8% vs. 0% for ensifentrine (Ohtuvayre) and placebo, respectively. There was a total of 14 deaths reported that were considered treatment-emergent but occurred across both ensifentrine and placebo arms.
V. The 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report defines diagnosis of COPD as any patient with a post-bronchodilator FEV1/FVC ratio of <0.7, along with characteristic symptoms such as dyspnea, cough or sputum production, and/or history of

exposure to risk factors (i.e. tobacco smoke, occupational contact, host factors). Spirometry also provides guidance on severity of airflow obstruction and disease.

Grade	Severity	FEV1 % predicted
GOLD 1	Mild	≥80
GOLD 2	Moderate	50-79
GOLD 3	Severe	30-49
GOLD 4	Very Severe	<30

VI. The modified Medical Research Council (mMRC) dyspnea scale provides a measure of breathlessness in patients with COPD and relates to other comprehensive health status measures such as the St. George's Respiratory Questionnaire (SGRQ). An mMRC score of ≥ 2 is considered the threshold for less or more breathlessness.

VII. As of the 2024 GOLD Report, the ABE Assessment Tool is a way to determine current disease severity and how to approach treatment based on symptom scores such as the mMRC, severity of airflow obstruction, and exacerbation history. Depending on the severity category, the recommended initial treatment includes a long-acting beta-adrenoceptor agonist (LABA) and/or long-acting muscarinic agent (LAMA) with, or without, an inhaled corticosteroid (ICS). If control is not achieved despite proper adherence to initial regimen, further recommendations include maximizing LAMA and LABA dual therapy, addition of ICS for triple therapy if needed, addition of a PDE inhibitor for patients experiencing increased exacerbations and maximizing non-pharmacological treatment. Treatment is focused on reducing symptoms and exacerbations and FEV1 change is considered a surrogate marker to assess disease decline rate. Long-acting beta-adrenoceptor agonist (LABA) and LAMA therapies are found to reduce rate of exacerbations alone or in combination.

VIII. Addition of ICS therapy to an existing regimen was found to have a greater impact on lung function and reduction of exacerbations vs. ICS alone. Inclusion of an ICS is primarily reserved for cases that have higher exacerbation rates per year, history of asthma, hospitalizations due to exacerbations and eosinophilic disease (blood eosinophils > 100 cells/µL). The benefits should outweigh the risks; addition of an ICS may cause increased risk of steroid-related diseases and increased risk of pneumonia.

IX. In both pivotal trials ensifentrine (Ohtuvayre) was studied as an add on to background therapies, (a mix of LABA or LAMA, with or without an ICS) in the majority of patients. Although background therapies did not reflect the guideline standard of dual LAMA/LABA or triple therapy (LAMA/LABA/ICS), ensifentrine (Ohtuvayre) is likely to be utilized as add-on therapy to LAMA/LABA ± ICS in real-world practice, given the need for additional treatment options in this setting.

Investigational Uses

I. Ensifentrine (Ohtuvayre) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   a. Asthma
      i. Ensifentrine (Ohtuvayre) was studied in a phase II, randomized, double-blind, placebo controlled seven-way crossover study (PMID: 31202957; NCT02427165) to assess the effect of a single dose of ensifentrine against placebo and salbutamol (a beta-2 agonist). Co-primary endpoints were peak and average

FEV1 over 12 hours compared to placebo and salbutamol. All active treatments were found superior to placebo with no significant difference between ensifentrine and salbutamol. The safety profile was similar to salbutamol. The treatments were seven separate visits with a 2–14-day washout period in between. Further studies are required to assess the true long-term efficacy and safety as a background asthma controller therapy.

b. Cystic Fibrosis
    i. A phase IIa, randomized, double blind, placebo controlled, three-way crossover study (NCT02919995) to assess the pharmacokinetics in adult patients with cystic fibrosis (CF). Interventions included two different doses of ensifentrine and placebo with the primary outcome as AUC by dose and maximum plasma concentration after each dose. Secondary outcome measures included FEV1 AUC at different time points. There was a dose-dependent correlation between drug concentration and AUC when comparing the higher to lower dose ensifentrine, while the time to maximum concentration was similar. The mean secondary peak FEV1 between all three treatments were similar. Further studies are needed to compare therapy with patients who are on standard of care CF medications to understand the true benefit as possibly an add-on treatment.
c. Non-Cystic Fibrosis Bronchiectasis
    i. This is currently in review for treatment of non-cystic fibrosis (non-CF) bronchiectasis. In theory, the dual anti-inflammatory and bronchodilator action can reduce cough and sputum symptoms along with reducing respiratory inflammation and exacerbations related to bronchiectasis. Further RCT studies are required to assess the long-term efficacy and safety versus placebo and/or other standard of care therapies.

References

1. Ohtuvayre [Prescribing Information]. London, UK and Raleigh, NC: Verona Pharma. June 2024.
2. Anzueto A, Barjaktarevic IZ, Siler TM, et al. Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease: Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials). Am J Respir Crit Care Med. 2023;208(4):406-416. doi:10.1164/rccm.202306-0944OCTitle
3. Global Initiative for Chronic Obstructive Lung Disease. 2024 REPORT Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease Global Initiative for Chronic Obstructive Lung Disease Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease.; 2024. https://goldcopd.org/wp-content/uploads/2024/02/GOLD-2024_v1.2-11Jan24_WMV.pdf
4. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014 Feb 1;189(3):250-5. doi: 10.1164/rccm.201310-1863PP. PMID: 24383418

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	Chronic Obstructive Pulmonary Disease (COPD)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2024

entrectinib (Rozlytrek®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP082

Description

Entrectinib (Rozlytrek) is an orally administered selective kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
entrectinib (Rozlyrek)	Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors Non-small cell lung cancer, metastatic, ROS1-positive	50 mg pellets	**Pediatric:** Dosing per body surface area* to the nearest full-size package
		100 mg capsules	30 capsules/30 days
		200 mg capsules	90 capsules/30 days

**See appendix for body surface area dosing for pediatric patients with NTRK positive solid tumors*

Initial Evaluation

I. **Entrectinib (Rozlytrek)** may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with an oncologist; **AND**
   B. Medication will not be used in combination with any other oncolytic medication; **AND**
   C. A diagnosis of one of the following:
      1. **Solid tumor with a confirmed NTRK gene fusion**; **AND**
         i. Member is one month of age or older; **AND**
         ii. If member is under the age of 18, the member's body surface area (BSA) is submitted; **AND**
         iii. Member has metastatic disease; **OR**
            a. Surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
         iv. Member does not have an acquired resistance mutation; **AND**
         v. Attestation that all alternative therapies for diagnosis and stage of cancer have been exhausted as defined by:
            a. Progression following all appropriate treatments; **OR**
            b. Nonresponse to all available therapies; **OR**
            c. All available therapies are contraindicated or not tolerated; **OR**

d. No standard or satisfactory treatments exist; **OR**

2. **ROS1-positive non-small cell lung cancer as detected by an FDA-approved test**; **AND**
    i. Member is 18 years of age or older; **AND**
    ii. Member has not progressed on any previous ROS1 targeted therapy [e.g., crizotinib (Xalkori), ceritinib (Zykadia), lorlatinib (Lorbrena), etc.]

II. Entrectinib (Rozlytrek) is considered investigational when used for all other conditions, including but not limited to:
    A. Non-small cell lung cancer without NTRK fusion or ROS1-positive gene rearrangements (e.g., ALK-positive NSCLC)
    B. Solid tumors that do not harbor NTRK gene fusions

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 any other oncolytic medication; **AND**
IV. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Entrectinib (Rozlytrek) is currently FDA approved for adult patients with a *ROS1*-positive metastatic non-small cell lung cancer (NSCLC) and received an accelerated approval in 2019 for adult and pediatric patients ages 12 and older for neurotrophic tyrosine receptor kinase (NTRK) positive solid tumors, metastatic or where surgical resection is likely to cause severe morbidity. In October 2023, this accelerated approval in NTRK solid tumors was expanded to include age one month and older.
II. Due to the complexity of treatment and diagnosis, of either indication, it is recommended that patients are seen by, or in consultation with an oncologist.
III. Neither therapy is approved to be used in combination with another oncolytic medication; therefore, entrectinib (Rozlytrek) should be used as monotherapy.
IV. Safety and efficacy data for entrectinib (Rozlytrek) is available through the following clinical trials: Phase 2 STARTRK-2, Phase 1 STARTRK-2, Phase 1 ALKA-372-001, and Phase 1/2 STARTRK-NG and TAPISTRY. The last two supporting approval in pediatric subjects.
    - STARTRK2: Basket study of entrectinib (Rozlytrek) for the treatment of patients with solid tumors harboring NTRK1/2/3, ROS1 or ALK gene rearrangements (fusions). This pivotal trial was non-randomized, open-label and analyzed 206 subjects for safety. For efficacy, data was captured for 51 NTRK fusion-positive and 37 ROS1-positive subjects.
    - STARTRK1: A Phase I, single-arm, open-label study evaluated the same population parameters as STARTRK2, and included 76 subjects for the safety evaluation. Two

subjects with NTRK fusion-positive and 7 subjects with ROS1-positive disease were evaluated for efficacy.

- ALKA-372-001: A Phase I, single-arm, open-label study evaluated the same population in STARTRK1 and 2. Safety data was gathered from 57 subjects. One subject had NTRK fusion-positive and 9 subjects had ROS1-positive disease were evaluated for efficacy.
- STARTRK-NG: A Phase I/IIb, single-arm, open-label study evaluated dose escalation and expansion in children and adolescents with recurrent or refractory solid tumors with or without TRK, ROS1, or ALK fusions. No subjects were included that had NTRK fusion-positive or ROS1-positive NSCLC. Twenty-nine subjects were evaluated. In 2023, this was expanded to include NTRK and ROS1 gene fusions; 15 subjects with NTRK 1/2/3 and eight with ROS1 were included in the primary outcomes.
- TAPISTRY: Phase 2, open-label, multi-cohort study in patients with locally advanced, unresectable, or metastatic solid tumors. This trial tests multiple different treatment arms and mutation types. For entrectinib (Rozlytrek), recruitment of 50 subjects for ROS1 arm and 200 patients for the NTRK arm is being projected. The trial does not conclude until 2032.

NTRK Positive Solid Tumors

V. Data for NTRK fusion-positive solid tumor FDA-approval for adult patients included a pooled group of 54 subjects across the trials listed above. Patients were mainly white, female with a median age of 58, and 96% of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer including surgery (n = 43), radiotherapy (n = 36), or systemic therapy (n = 48). Forty patients (74%) received prior systemic therapy for metastatic disease with one prior systemic regimen and 17% (n = 9) received 3 or more prior systemic regimens. The primary outcome was an objective response rate (ORR) of: 59% (43-71), with 46% achieving partial response (PR) and 13% achieving complete response (CR).

VI. Data for NTRK fusion positive solid tumor in pediatric patients included 33 patients from the last two trials listed above. Patients were on average four years of age, white with locally advanced disease (71%) or metastatic disease (29%) with 85% of patients having prior therapy for their cancer including surgery (n=20), radiotherapy (n=7) and/or systemic therapy (n=22). The primary endpoint was ORR which was 70% (51-84) with 27% having a partial response (PR) and 42% having a complete response (CR).

ROS1-positive NSCLC

VII. Data for ROS1-positive NSCLC FDA-approved included a pooled 92 subjects across the trials listed above with the primary outcome of ORR: 74% (64-83), 59% with PR and 15% CR.

VIII. NTRK fusions are found in a wide variety of cancers and are generally mutually exclusive from other targetable oncogenic drivers. There is a lack of standard of care and these patients are generally treated according to the histological tumor type and do not have targeted therapy. There is only one other agent, larotrectinib (Vitrakvi), for a similar setting to entrectinib (Rozlytrek). It was FDA-approved less than one year before entrectinib (Rozlytrek) in November 2018. The medication was evaluated in those that had progressed following treatment or had no satisfactory treatment alternative(s). Additionally, subjects that had metastatic disease or surgical resection were likely to result in severe morbidity.

IX. ROS1-positive NSCLC is a rare subtype of NSCLC, accounting for only 1-2% of all cases. ROS1-positive NSCLC is a progressive disease with the most common site of metastases being the CNS. Currently, the NCCN 1.2024 NSCLC guidelines recommend entrectinib, crizotinib, repotrectinib or ceritinib as preferred therapy for ROS1- positive NSCLC. Crizotinib (Xalkori) is FDA-approved, but has limited data for safety and efficacy and has not been shown to target CNS metastases. Ceritinib (Zykadia) has been used in some instances, which may have more CNS activity; however, safety and efficacy data is very limited and it is not FDA-approved for ROS1-positive NSCLC. Repotrectinib (Augtyro) did allow those with CNS activity in the study as long as stable, responses were shown in seven of the eight patients. Entrectinib (Rozlytrek) has shown some CNS activity, and in clinical trials five of seven subjects with CNS metastases showed CNS response.

X. In clinical trials dose interruption occurred in 46% of subjects, and dose reduction was required in 28%. Grade 3-4 adverse drug events occurred in 60% of subjects in the trial.

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.

Investigational or Not Medically Necessary Uses

I. Entrectinib (Rozlytrek) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Non-small cell lung cancer without NTRK fusion or ROS1-positive gene rearrangements (e.g., ALK-positive NSCLC)
      i. Due to the mechanism of action, investigation in ALK-positive NSCLC is underway; however, safety and efficacy have not been defined.
   B. Solid tumors that do not harbor NTRK gene fusions
      i. Efficacy and safety of entrectinib (Rozlytrek) in solid tumors without NTRK fusions has not been sufficiently evaluated.

Appendix

I. Table 1: Pediatric dosing for NTRK gene fusion positive solid tumors

Body Surface Area (BSA)	Recommended Dosage, Orally, once daily
≤0.5 m^2	300 mg/m^2
0.51 to 0.80 m^2	200 mg
0.81 to 1.10 m^2	300 mg
1.11 to 1.50 m^2	400 mg
≥1.51 m^2	600 mg

- In general, the average BSA for a newborn child is 0.25m^2; a two- year-old is 0.5m^2; a five-year-old child is 0.77m^2; a ten-year-old child is 1.14m^2.

References

1. Rozlytrek [Prescribing Information]. Genentech. San Francisco, CA. 2024.
2. Farago AF, Le LP, Zheng Z, et al. Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small Cell Lung Cancer. J Thorac Oncol. 2015;10(12):1670-4.
3. Sigal D, Tartar M, Xavier M, et al. Activity of Entrectinib in a Patient With the First Reported Fusion in Neuroendocrine Cancer. J Natl Compr Canc Netw. 2017;15(11):1317-1322.
4. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol. 2019;32(1):147-153.
5. Vitrakvi [Prescribing Information]. Loxo Oncology, Inc. Stamford, CT. 2023
6. Xalkori [Prescribing Information]. Pfizer Labs. 2023.
7. Augtyro [Prescribing Information]. Bristol Myers Squibb. Princeton, NJ. 2023.
8. Demetri, G.D., et al., Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: Pooled analysis of STARTRK-2, STARTRK-1, and ALKA-372- 001. Ann Oncol, 2018. 29(S9).
9. National comprehensive Cancer Network. NCCN Guidelines. Soft Tissue Sarcoma: Version 3.2023. Available at: sarcoma.pdf (nccn.org)
10. Desai AV, Robinson GW, Gauvain K, et al. Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). *Neuro Oncol*. 2022;24(10):1776-1789.

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
larotrectinib (VITRAKVI®)	NTRK Gene Fusion Positive Solid Tumors
ALK+ Inhibitors	Non-Small Cell Lung Cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial approval duration from three months to six months. Updated new age expansion for NTRK positive solid tumors in patients one month and older. Removal of specialist requirement upon renewal, removal of toxicity assessment upon renewal, and addition of standard sample renewal language. Updated supporting evidence across all indications. Updated references and added related policy table.	02/2024
Removed split fill requirement	10/31/22
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Previous Reviews	09/2019 11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP023

Split Fill Management* (applies to dacomitinib [Vizimpro], erlotinib [Tarceva], and lazertinib [Lazcluze] only)

Description

Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) are orally administered epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKIs).

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
osimertinib (Tagrisso)	Non-Small Cell Lung Cancer (NSCLC), resectable early stage with EGFR exon 19 or 21 L858R mutation; Non-Small Cell Lung Cancer (NSCLC), unresectable, stage III, with EGFR exon 19 or 21 L858R mutation Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation	40 mg tablets	30 tablets/30 days
		80 mg tablets	
dacomitinib (Vizimpro)	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	15 mg tablets	30 tablets/30 days
		30 mg tablets	
		45 mg tablets	
generic erlotinib	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation; Pancreatic cancer, advanced or metastatic	25 mg tablets	90 tablets/30 days
		100 mg tablets	30 tablets/30 days
	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation;	150 mg tablets	30 tablets/30 days
erlotinib (Tarceva)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation;	25 mg tablets	90 tablets/30 days
		100 mg tablets	30 tablets/30 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

	Pancreatic cancer, advanced or metastatic		
	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation;	150 mg tablets	30 tablets/30 days
afatinib (Gilotrif)	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	20 mg tablets	30 tablets/30 days
		30 mg tablets	
		40 mg tablets	
gefitinib (Iressa)	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	250 mg tablets	30 tablets/30 days
generic gefitinib	Non-Small Cell Lung Cancer (NSCLC), metastatic with EGFR exon 19 or 21 L858R mutation	250 mg tablets	30 tablets/30 days
lazertinib (Lazcluze)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with EGFR exon 19 or 21 L858R mutation	80 mg tablet	60 tablets/30 days
		240 mg tablet	30 tablets/30 days

Initial Evaluation

I. **Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (generic Iressa), gefitinib (Iressa), and lazertinib (Lazcluze)** 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; **AND**
   C. The medication will not be used in combination with any other oncology therapy unless outlined in policy; **AND**
      1. **The request if for osimertinib (Tagrisso); AND**
         i. The member has early stage (stage IB-IIIA) non-small cell lung cancer; **AND**
            a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
            b. The member has <u>not</u> had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase (TKI) therapy; **AND**
            c. The member has undergone complete tumor resection; **AND**
            d. The treatment will be used as adjuvant therapy; **AND**
            e. The member has been previously treated with platinum-based chemotherapy (e.g., cisplatin); **OR**
               i. Platinum-based chemotherapy (e.g., cisplatin) is contraindicated or not tolerated; **OR**
         ii. The member has locally advanced, unresectable (stage III) non-small cell lung cancer; **AND**
            a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**

b. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase (TKI) therapy; **AND**
c. The member has not progressed during or following concurrent or sequential platinum-based chemoradiation; **OR**

iii. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
a. Treatment will be used in combination with pemetrexed and platinum-based chemotherapy; **OR**
i. Medication will be used as monotherapy; **AND**
b. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
i. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
1. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **OR**
ii. Confirmation of epidermal growth factor receptor (EGFR) T790 mutation; **AND**
1. Documented disease progression on previous epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**

2. The request is for **dacomitinib (Vizimpro); AND**
i. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
ii. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
iii. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
iv. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
v. The member does not have brain metastases; **OR**

3. The request is for **erlotinib (Tarceva); AND**
i. Generic erlotinib is prescribed; **OR**
a. The member has tried and failed, has a contraindication to, or intolerance to generic erlotinib; **AND**
ii. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
b. The member has not had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
c. The treatment will be used for first-line, maintenance, second-line, or greater-line treatment, and may have progressed after previous chemotherapy; **OR**

iii. The member has locally advanced, unresectable or metastatic (stage IV), pancreatic cancer; **AND**
    a. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
    b. Treatment will be used in combination with gemcitabine; **OR**

4. The request is for **afatinib (Gilotrif); AND**
    i. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
        a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation, or L861Q, G719X, or S7681 mutation; **AND**
        b. The member has <u>not</u> had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
        c. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **OR**
            i. The member had disease progression on platinum-based chemotherapy (e.g., cisplatin, carboplatin, etc.); **OR**
    ii. Metastatic, squamous non-small cell lung cancer that has progressed on or after treatment with platinum-based chemotherapy (e.g., cisplatin, carboplatin, etc.)
5. The request is for **gefitinib (generic Iressa)** or **BRAND gefitinib (Iressa); AND**
    i. Generic gefitinib is prescribed; **OR**
        a. The member has tried and failed, has a contraindication to, or intolerance to generic gefitinib; **AND**
    ii. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
        a. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
        b. The member has <u>not</u> had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase (TKI) therapy; **AND**
        c. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **OR**
6. The request is for **lazertinib (Lazcluze); AND**
    i. The member has locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
    ii. The medication is being prescribed as a first-line systemic therapy in the locally advanced or metastatic setting; **AND**
    iii. The member has <u>not</u> had disease progression on prior epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) therapy; **AND**
    iv. Confirmation of epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**
    v. Treatment will be used in combination with amivantamab (Rybrevant)*; **AND**
        a. Provider attestation that prophylactic anticoagulation (e.g., apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran, enoxaparin,

etc.) will be concomitantly administered for the first four months of treatment; **AND**

vi. There are no evident central nervous system (CNS) metastases; **AND**
    a. Documentation of intolerance or contraindication to osimertinib (Tagrisso)*, erlotinib (Tarceva)*, gefitinib (Iressa)*, afatinib (Gilotrif)*, and dacomitinib (Vizimpro)*; **OR**

vii. There are central nervous system (CNS) metastases; **AND**
    a. Documentation of intolerance or contraindication to osimertinib (Tagrisso)*

**Please note: medications notated with an asterisk may require additional review*

II. Dacomitinib (Vizimpro) is considered not medically necessary when criteria above are not met and/or when used for:
    A. The treatment of non-small cell lung cancer (NSCLC) in the second line setting

III. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) are considered investigational when used for all other conditions, including but not limited to:
    A. Dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) used in combination with any other treatment including chemotherapy or targeted agent
    B. Early-stage epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC) with agents other than osimertinib (Tagrisso)
    C. Lazertinib (Lazcluze) monotherapy in non-small cell lung cancer (NSCLC) with T790M mutation
    D. Lazertinib (Lazcluze) in non-small cell lung cancer (NSCLC) with mesenchymal epithelial transition factor receptor (MET) overexpression
    E. Pancreatic cancer
    F. Squamous non-small cell lung cancer (NSCLC)
    G. Head and neck cancer
    H. Renal cell carcinoma
    I. Bone cancer including, but not limited to, chordoma
    J. Central nervous system cancers without primary tumor source of non-small cell lung cancer (NSCLC)
    K. Hepatobiliary cancers

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; **AND**

III. The medication will not be used in combination with any other agent listed in this policy, or another medication for the oncolytic condition being treated; **OR**
    - The request is for erlotinib (Tarceva) in combination with gemcitabine for the treatment of pancreatic cancer; **OR**

- The request is for osimertinib (Tagrisso) in combination with platinum-based chemotherapy (e.g., cisplatin) for non-small cell lung cancer with EGFR exon 19 or 21 L858R mutation; **OR**
- The request is for lazertinib (Lazcluze) in combination with amivantamab (Rybrevant)* for non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 or 21 L858R mutation; **AND**

IV. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**

V. If the request is for brand erlotinib (Tarceva), generic erlotinib has not been tolerated or is contraindicated; **OR**

VI. If the request is for brand gefitinib (Iressa), generic gefitinib has not been tolerated or is contraindicated

Supporting Evidence

I. Lung cancer is the second most common cancer diagnosed in the U.S. and is the leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) represents up to 85% of lung cancer diagnoses and EGFR mutations occur in up to one-third of patients with NSCLC. Epidermal growth factor receptor exon 19 deletions or exon 21 L858R substitution mutations make up around 90% of all EGFR mutations.

II. Given the complexity of management of NSCLC and pancreatic cancer, the treatment of NSCLC and pancreatic cancer must be initiated by, in or consultation with, an oncologist.

III. The National Comprehensive Cancer Network (NCCN) guidelines for treatment of Non-Small Cell Lung Cancer have been updated to include lazertinib (Lazcluze) in combination with amivantamab (Rybrevant). The National Cancer Center Network (NCCN) recommends osimertinib (Tagrisso) monotherapy (category 1, preferred), osimertinib (Tagrisso) with chemotherapy, and lazertinib (Lazcluze) in combination with amivantamab (Rybrevant) (category 1, other recommendation) as first line therapy in patients who have EGFR exon 19 deletion or exon 21 L858R mutations. The National Cancer Center Network (NCCN) guidelines also note erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and dacomitinib (Vizimpro) monotherapy may be useful in certain circumstances in the first line setting (category 1).

Osimertinib (Tagrisso)

IV. Osimertinib (Tagrisso) is FDA-approved for treatment of early stage (IIB-IIIA) NSCLC with exon 19/21 L858R mutation as adjuvant therapy after complete tumor resection, treatment of stage III, unresectable NSCLC with exon 19/21 mutation after completion of chemoradiation, in the first line setting for metastatic NSCLC with exon 19/21 L858R mutation (with or without platinum-based chemotherapy), and in the second-line setting for metastatic NSCLC with T790M mutation.

- Osimertinib (Tagrisso) was studied in the FLAURA trial, which included 556 treatment naïve participants with EGFR NSCLC. Osimertinib (Tagrisso) was compared to gefitinib or erlotinib. Osimertinib (Tagrisso) demonstrated improvement in progression free survival (PFS), median PFS 18.9 months vs 10.2 months in the osimertinib (Tagrisso) arm vs gefitinib/erlotinib, hazard ratio (HR) 0.46 (95% CI, 0.37 to 0.57, P<0.001). Mature overall survival (OS) was in favor of osimertinib (Tagrisso) compared to gefitinib/erlotinib, 38.6 months vs 31.8 month, HR 0.8 (95% CI, 0.64 to 1, P=0.046). The safety profile was favorable compared to studied EGFR TKIs. Osimertinib (Tagrisso) showed greater intracranial efficacy and tolerability.

- Tumors that progress on TKIs are found to have a substitution of methionine for threonine at position 790 (T790M) mutation on exon 20. Osimertinib (Tagrisso) has been demonstrated to have efficacy in patients with this mutation. Currently, there is no evidence for safety or efficacy in the second line setting for osimertinib (Tagrisso) in absence of this mutation and the medication shall not be used.
- Osimertinib (Tagrisso) demonstrated disease free survival for patients with stage IB-IIIA disease NSCLC with exon 19-21 mutation in the Phase 3 (ADAURA) trial. Mature OS data was in favor of osimertinib (Tagrisso) compared to placebo, HR 0.17 (95% CI, 0.11 to 0.26); P < 0.001. Patients were excluded from the trial if they had received any prior EGFR-TKI therapy. Safety of osimertinib (Tagrisso) in this population is unknown, and efficacy would not be expected in this setting after progression on another agent within the same class. All patients had the EGFR exon 19 or exon 21 L858R mutation, and all patients had undergone complete (negative margins) surgical resection of NSCLC tumors. The majority of patients (76%) with stage II-IIIA disease had received previous adjuvant platinum-based chemotherapy, as well as 25% of those with stage IB disease (53% had received prior platinum therapy overall). Use of previous platinum-based chemotherapy is not required by the FDA-approved indication; however, NCCN guidelines make a category 1 recommendation for osimertinib (Tagrisso) as adjuvant therapy for treatment of stage IB-IIIA NSCLC with exon 19-21 mutation after receiving previous adjuvant chemotherapy or in patients that are ineligible to receive platinum-based chemotherapy.
- In the Phase 3, double-blind, placebo-controlled trial (LAURA), osimertinib (Tagrisso) demonstrated significantly longer progression-free survival than placebo in patients with unresectable stage III *EGFR*-mutated NSCLC who had not progressed during or following concurrent or sequential platinum-based chemoradiation, 39.1 vs 5.6 months, PFS HR 0.16 (95% CI, 0.10 to 0.24; P<0.001). Interim OS data (maturity, 20%) showed 36-month overall survival among 84% of patients with osimertinib (95% CI, 75 to 89) and 74% with placebo (95% CI, 57 to 85), with a HR for death of 0.81 (95% CI, 0.42 to 1.56; P=0.53). The most common adverse events, irrespective of cause, were radiation pneumonitis (48% with osimertinib vs. 38% with placebo), diarrhea (36% vs. 14%), and rash (24% vs. 14%). Adverse events of grade 3 or higher were reported in 50 patients (35%) with osimertinib and 9 patients (12%) with placebo. PFS and ORR endpoints are surrogate markers that do not directly measure clinical outcomes that predict morbidity or mortality. OS was not yet matured at PFS read out but no trend towards a detriment was observed. PFS is a surrogate endpoint and TKI studies have not demonstrated a strong positive correlation between PFS and OS in NSCLC with EGFR mutation and the quality of evidence is considered low.
- The Phase 3, open-label, randomized trial (FLAURA2) evaluated efficacy of osimertinib (Tagrisso) plus platinum-based chemotherapy versus osimertinib (Tagrisso) monotherapy, in treatment of patients with advanced or metastatic NSCLC with exon 19-21 L858R mutation who had not previously received treatment for advanced disease. A total of 557 participants were randomized 1:1 (stratified by race) to receive osimertinib (80 mg once daily) with chemotherapy (pemetrexed [500 mg per square meter of body-surface area] plus either cisplatin [75 mg per square meter] or carboplatin [pharmacologically guided dose]) or to receive osimertinib monotherapy (80 mg once daily). Participants were 18 years and older

and central nervous system (CNS) metastases were permitted if neurologically stable. The median age was 61 years, 61% were female; 64% were Asian and 66% were never smokers. Osimertinib (Tagrisso) plus platinum-based chemotherapy demonstrated a significantly longer PFS compared to osimertinib (Tagrisso) monotherapy HR 0.62 (95% CI, 0.49 to 0.79, p<0.001). OS was not mature at PFS data cutoff but favored the osimertinib (Tagrisso) plus chemotherapy group compared to osimertinib (Tagrisso) monotherapy, 79% (95% CI, 73 to 83) and 73% (95% CI, 67 to 78). Adverse events of grade 3 or higher were reported in 176 patients (64%) in the osimertinib–chemotherapy group and in 75 (27%) in the osimertinib group. The most common adverse events were anemia, diarrhea, nausea, and decreased appetite. There is uncertainty in the clinical meaningfulness of PFS as it is a surrogate endpoint that has not been correlated with clinically meaningful outcomes such as morbidity and mortality in NSCLC with EGFR mutations. The quality of evidence is considered low due to the lack of blinding and use of surrogate endpoints.

Dacomitinib (Vizimpro)

V. Dacomitinib (Vizimpro) is FDA-approved for the treatment of adults with metastatic non-small cell lung cancer with EGFR exon 19 or 21 deletion mutation.

VI. The efficacy and safety of dacomitinib (Vizimpro) was demonstrated in an open-label trial that assessed dacomitinib (Vizimpro) in the first-line, metastatic disease, treatment naïve, monotherapy setting. Patients were excluded if they had previous use of another EGFR TKI and/or presence of brain metastases. Dacomitinib (Vizimpro) was compared against gefitinib (Iressa), and showed an improvement in PFS.

VII. Dacomitinib (Vizimpro) has been studied in the second-line setting, as well as in non-small cell lung cancer with undetermined mutational status; however, the trials showed no improvement in outcomes compared to erlotinib (Tarceva) or placebo.

Erlotinib (Tarceva)

VIII. Erlotinib (Tarceva) was evaluated in the OPTIMAL, EURTAC, and ENSURE trials versus chemotherapy. Objective response rates (ORR) and PFS were favorable for erlotinib (Tarceva).

IX. Erlotinib (Tarceva) was evaluated in combination with gemcitabine for pancreatic cancer. Results of phase III studies have indicated an increase in survival compared to gemcitabine alone; however, grade I and II adverse events are expected to occur at greater frequency with combination therapy.

Afatinib (Gilotrif)

X. Afatinib (Gilotrif) was evaluated in the LUX clinical trials program versus chemotherapy and showed an increase in PFS as well as time to symptom progression and quality of life. Afatinib (Gilotrif) is also FDA-approved for S761I, L861Q, and G719X mutations.

XI. Afatinib (Gilotrif) was evaluated in an RCT versus erlotinib (Tarceva) for previously treated, metastatic, squamous NSCLC. The results were favorable for afatinib (Gilotrif) over erlotinib (Tarceva) in PFS and OS.

Gefitinib (Iressa)

XII. Gefitinib (Iressa) showed favorable PFS against chemotherapy in several RCTs.

XIII. Treatment of EGFR TKI for NSCLC shall be individualized based on provider and patient preferences, and disease characteristics. There have been several trials comparing agents in this policy. Gefitinib (Iressa) has shown comparable efficacy to erlotinib (Tarceva) and afatinib (Gilotrif) and may modestly improve outcomes over gefitinib (Iressa); however, it may increase risk of serious toxicities as well.

XIV. 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.

Lazertinib (Lazcluze)

XV. Lazertinib (Lazcluze) was studied in a Phase 3, randomized study (MARIPOSA). The study included 1,074 participants 18 years and older with confirmed locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations. Participants were treatment naïve for advanced disease and randomized to receive lazertinib (Lazcluze) 240mg daily plus amivantamab (Rybrevant) 1050mg (if <80kg) or 1400mg (if >80kg) intravenously once weekly for five weeks, then every two weeks, osimertinib (Tagrisso) 80mg daily, or lazertinib (Lazcluze) 240mg daily. The lazertinib (Lazcluze) combination arm was unblinded while the osimertinib (Tagrisso) and lazertinib (Lazcluze) arms were blinded. Baseline characteristics were similar between both groups: median age 63 years, mostly female (60%), 89% Asian, 41% brain metastases, 60% exon 19 deletion, and 40% exon 21 L858R mutation. The primary endpoint of progression free survival (PFS) was statistically significant, favoring the lazertinib (Lazcluze) plus amivantamab (Rybrevant) group compared to osimertinib (Tagrisso), 23.7 months vs 16.6 months, difference of 7.1 months, HR 0.70 (0.58-0.85), p <0.001. Overall survival was not mature at the time of PFS readout. Objective response rate was 86% vs 85% in the lazertinib (Lazcluze) plus amivantamab (Rybrevant) group vs osimertinib (Tagrisso). Recent study updates from May 2024 provided by the FDA demonstrate that OS is trending in favor of lazertinib (Lazcluze) in combination with amivantamab (Rybrevant), HR 0.77 (95% CI, 0.61-0.96) at 82% maturity, compared to osimertinib (Tagrisso). However, interim OS data is considered descriptive. The quality of evidence is considered low due to the lack of blinding and use of surrogate endpoints. It is unknown how lazertinib (Lazcluze) in combination with amivantamab (Rybrevant) compares to other osimertinib (Tagrisso) with chemotherapy or other TKIs.

1. Lazertinib (Lazcluze) demonstrated significantly more adverse events compared to osimertinib (Tagrisso). Grade 3 or higher adverse events were reported in 75% of the patients treated with lazertinib (Lazcluze) plus amivantamab (Rybrevant) and in 43% of those treated with osimertinib (Tagrisso). Paronychia (11% vs <1%) and rash (15% vs 1%) were the most common adverse events. Venous thromboembolism (VTE) adverse events were reported in 37% of the patients in the lazertinib (Lazcluze) plus amivantamab (Rybrevant) arm and in 9% of those in the osimertinib (Tagrisso) arm.

XVI. The National Comprehensive Cancer Network (NCCN) guidelines recommend osimertinib (Tagrisso) monotherapy as a preferred first-line regimen compared to lazertinib (Lazcluze) plus amivantamab (Rybrevant) (both category 1). The National Comprehensive Cancer Network (NCCN) also makes a category 1 recommendation for erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and dacomitinib (Vizimpro) as first line treatment for NSCLC with exon 19/21 mutation. In the absence of direct comparison data demonstrating inferiority of specific EGFR TKIs, for lazertinib (Lazcluze), requiring treatment with osimertinib (Tagrisso), erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and dacomitinib (Vizimpro) in members with no CNS involvement, is clinically appropriate and cost effective. Guidelines acknowledge that osimertinib (Tagrisso) and lazertinib (Lazcluze) have brain-penetrant properties, as such treatment with osimertinib (Tagrisso) is required for members presenting with CNS metastases.

Investigational or Not Medically Necessary Uses

I. Dacomitinib (Vizimpro) was evaluated versus placebo and erlotinib (Tarceva) in the second-line setting; however, the trials showed no improvement in outcomes compared to erlotinib (Tarceva) or placebo.

II. The agents in this policy have not been sufficiently evaluated in the following settings. Some data may be available or may be recommended by NCCN; however, safety and efficacy have not been established:
    A. Dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (Iressa), and lazertinib (Lazcluze) used in combination with any other treatment including chemotherapy or targeted agent
    B. Early stage epidermal growth factor receptor (EGFR) non-small cell lung cancer (NSCLC)outside of osimertinib (Tagrisso)
    C. Lazertinib (Lazcluze) monotherapy in non-small cell lung cancer (NSCLC) with T790M mutation
    D. Lazertinib (Lazcluze) in non-small cell lung cancer (NSCLC) with mesenchymal epithelial transition factor receptor (MET) overexpression
    E. Pancreatic cancer
    F. Squamous non-small cell lung cancer (NSCLC)
    G. Head and neck cancer
    H. Renal cell carcinoma
    I. Bone cancer including, but not limited to, chordoma
    J. Central nervous system cancers without primary tumor source of non-small cell lung cancer (NSCLC)
    K. Hepatobiliary cancers

** 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. Wu YL., Tsuboi M., He J., et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2020;383(18):1711-1723.
2. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018;378(2):113-125.
3. Tagrisso [Prescribing Information]. Wilmington, DE: AstraZeneca, December 2020.
4. Ramalingam SS, Reungwetwattana T, Chewaskulyong B, et al. Osimertinib versus standard-of-care EGFR-TKI as first-line treatment in patients with EGFRm advanced NSCLC: FLAURA [abstract] [abstract]. Presented at the ESMO Congress; Madrid. Abstract LBA2_PR
5. Vizimpro [Prescribing Information]. New York, NY: Pfizer, September 2018.
6. Wu YL., Cheng Y., Zhou X., et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomized, open-label, phase 3 trial. Lancet Oncol 2017, published online September 25, 2017.
7. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011;12(8):735-42.

8. Zhou C, Wu YL, Chen G, et al. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). Ann Oncol. 2015;26(9):1877-83.
9. Urata Y, Katakami N, Morita S, et al. Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L. J Clin Oncol. 2016;34(27):3248-57.
10. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol. 2012;13(5):528-38.
11. Park K, Tan EH, O'byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016;17(5):577-89.
12. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-8.
13. Yang JJ, Zhou Q, Yan HH, et al. A phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. Br J Cancer. 2017;116(5):568-574.
14. Paz-ares L, Tan EH, O'byrne K, et al. Afatinib versus gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb LUX-Lung 7 trial. Ann Oncol. 2017;28(2):270-277.
15. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960-1966. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17452677.
16. Singhal N, Kotasek D, Parnis FX. Response to erlotinib in a patient with treatment refractory chordoma. Anticancer Drugs 2009;20(10):953-955
17. Gordon MS, Hussey M, Nagle RB, et al. Phase II study of erlotinib in patients with locally advanced or metastatic papillary histology renal cell cancer: SWOG S0317. J Clin Oncol 2009;27:5788-5793. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884559
18. Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol 2015;16:5
19. Planchard D, Jänne PA, Cheng Y, et al. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med. 2023;389(21):1935-1948.
20. Lazcluze (lazertinib) [prescribing information]. Horsham, PA: Janssen Biotech Inc; August 2024.
21. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer. NCCN. January 14, 2025. Accessed January 14, 2025. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
22. Cho BC, Lu S, Felip E, et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med. 2024;391(16):1486-1498.
23. Lu S, Ramalingam SS. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. Reply. N Engl J Med. 2024;391(16):1555-1556.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added lazertinib (Lazcluze) to policy and updated QL table to detail specific indications. Included a path to coverage for osimertinib (Tagrisso) in combination with platinum-based chemotherapy for first line treatment of NSCLC with exon 19/21 L858R. Added criteria for osimertinib (Tagrisso) in stage III, unresectable, NSCLC with EGFR exon 19/21 mutation, after chemoradiation. Updated format of criteria.	02/2025
Added generic erlotinib to QL table	01/2024
Added gefitinib (generic Iressa) to the policy; required step through generic gefitinib prior to use of branded Iressa; updated to match current policy formatting	07/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy updated to include osimertinib (Tagrisso) indication of early stage, adjuvant treatment to surgical resection in NSCLC.	01/2021
Criteria update and policy creation: All EGFR TKI agents combined into one policy, streamline quantity limits, renewal criteria, duration or approval upon initial and renewal request. Update Tagrisso criteria to allow for use in the first line setting. Addition of age requirement and prescriber requirement for all agents.	07/2019
Gilotrif criteria update: updated criteria to include L861Q, G719X, or S768I mutations and metastatic, squamous NSCLC that has progressed after treatment with platinum-based chemotherapy. Due to the statement that afatinib is not recommended as second-line therapy for squamous cell carcinoma from	03/2018

National Comprehensive Cancer Network (NCCN), a clinical note has been added to address the request for afatinib in members who are diagnosed with squamous NSCLC that has progressed on platinum-based chemotherapy. Tagrisso criteria update: Include clinical note regarding the Flaura trial and recent NCCN NSCLC Guidelines. Also, a route for approval if patient has a contraindication to erlotinib, afatinib and gefitinib.	
Gilotrif criteria update: updated criteria to new format, deleted renal and hepatic function questions, and deleted female contraception questions as this is properly managed by providers	01/2018
Previous reviews	12/2015, 01/2015, 09/2013, 05/2013, 11/2012, 03/2012, 03/2012, 10/2008, 04/2007
Criteria created	09/2005

eplontersen (Wainua™)
UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP303

Description
Eplontersen (Wainua) is a subcutaneously administered antisense oligonucleotide inhibitor.

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

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
eplontersen (Wainua)	Hereditary transthyretin amyloidosis (hATTR) with polyneuropathy	45 mg/0.8 mL auto-injector	0.8mL/28 days

Initial Evaluation

I. **Eplontersen (Wainua)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist or cardiologist; **AND**
   B. Member is 18 years of age or older; **AND**
   C. Medication is not used in combination with any other TTR silencer therapy (i.e., inotersen (Tegsedi), patisiran (Onpattro), tafamidis meglumine (Vyndaqel)); **AND**
   D. A diagnosis of **hereditary transthyretin amyloidosis (hATTR) with polyneuropathy** confirmed by:
      1. Documentation of amyloid deposit via biopsy; **AND**
      2. Documentation of transthyretin variant (TTR mutation) by genotyping (e.g., V30M); **AND;**
      ~~3.~~ Confirmation of <u>one</u> of the following baseline measures:
         i. A baseline polyneuropathy disability (PND) score less than, or equal to, IIIb; **OR**
         ii. A baseline Coutinho stage score less than, or equal to, two; **AND**
   E. Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); **AND**
   F. Member has <u>not</u> received or is not anticipating a liver transplant; **AND**
   G. Member does <u>not</u> have New York Heart Association (NYHA) functional class ≥ III heart failure

II. Eplontersen (Wainua) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Cardiac amyloidosis due to wild-type or mutant TTR.
   B. Transthyretin amyloidosis of the wild-type origin (ATTRwt)
   C. Pediatrics and adolescents under the age of 18 years old

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

D. When used in combination with other TTR silencer therapy (i.e., inotersen (Tegsedi), patisiran (Onpattro), tafamidis meglumine (Vyndaqel)).

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 the patient has experienced a positive clinical response to eplontersen (Wainua) (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); **AND**
IV. Continued confirmation of <u>one</u> of the following:
    A. Polyneuropathy disability (PND) score less than or equal to stage IIIb; **OR**
    B. Coutinho stage score less than or equal to two; **AND**
V. Eplontersen (Wainua) will not be used in combination with other with other therapies for hATTR (i.e., patisiran (Onpattro) or tafamidis meglumine (Vyndaqel); **AND**
VI. Member has <u>not</u> received or is not anticipating a liver transplant; **AND**
VII. Member does <u>not</u> have New York Heart Association (NYHA) functional class ≥ III heart failure

Supporting Evidence

I. Hereditary transthyretin amyloidosis (hATTR) with polyneuropathy is a rare, inherited disease that occurs due to mutations in the gene encoding transthyretin (TTR). Inherited mutations of the TRR gene are categorized into two main phenotypes: ATTRv with polyneuropathy (ATTRv-PN) and ATTRv with cardiomyopathy (ATTRv-CM). Eplontersen (Wainua) is currently approved for ATTRv-PN only.
II. Hereditary transthyretin amyloidosis is a systemic, progressively debilitating, and fatal disease caused by the misfolding, deposition, and accumulation of transthyretin (TTR) amyloid fibrils in multiple organs. Clinical course is variable and typically includes increased multiorgan involvement with progression of disease. Median survival is about ten years from disease onset. The goals of treatment include preventing disease progression, treating multiorgan involvement, reducing function loss, and preserving quality of life.
III. Eplontersen (Wainua) was studied in a Phase 3, multicenter, open-label, randomized, 6:1, historical placebo-controlled trial consisting of 144 subjects (NEURO-TTRansform study). Subjects included in the interim analysis had stage one or two ATTRv-PN (defined by either Coutinho staging or polyneuropathy disability [PND] score). Participants were excluded if they had received previous treatment with TRR silencers or had previously undergone a liver transplant. The mean subject age was 53 years, the majority being male, with V30M genetic mutation, stage one ATTRv-PN, less severe mobility at baseline, of non-US geographical region, and of the mixed cardiomyopathy phenotype.
IV. There are currently no official evidence-based guidelines specifically for the diagnosis of ATTRv-PN in the U.S. The American College of Cardiology (ACC) 2023 guidelines recommend diagnosis of ATTRv with a cardiologist as the designated primary clinician. The American Heart Association

(AHA) 2020 guidelines also recommend diagnosis and treatment under either a neurologist or cardiologist.

V. Safety and efficacy of eplontersen (Wainua) use in patients under the age of 18 has not been well-established. There is currently a lack of sufficient evidence or additional scientific literature to support the use of eplontersen (Wainua) in members under 18 years of age.

VI. Safety and efficacy of using eplontersen (Wainua) in combination with other TTR silencer therapies for hATTR (i.e., patisiran (Onpattro) or tafamidis meglumine (Vyndaqel) has not been studied. There is currently a lack of sufficient evidence or additional scientific literature to support the use of eplontersen (Wainua) in combination with other TTR silencer therapy.

VII. The American Heart Association (AHA) and American College of Cardiology (ACC) guideline recommendations for the diagnosis of amyloidosis are specific for the cardiomyopathy phenotype. The Journal of Neurology (2020) offers expert consensus recommendations specifically for the diagnosis of ATTRv-PN. Diagnosis of the hereditary form of ATTR requires deoxyribonucleic acid (DNA) sequencing and a biopsy. Deoxyribonucleic acid sequencing reveals the TTR gene mutation indicative of hereditary versus wild-type forms of ATTR. A biopsy is required to detect the presence of amyloid fibrils. Deoxyribonucleic acid sequencing and biopsy results are definitive for confirmation of hATTR. Eplontersen (Wainua) is not FDA-indicated for use in wild-type amyloidosis.

VIII. The Journal of Neurology recommends staging of ATTRv-PN with either the Coutinho staging score or the polyneuropathy disability (PND) staging score to assess for mobility, ambulation, and neuropathy severity. The NEURO-TTRansform study only included subjects that had earlier, less severe forms of ATTRv-PN (defined by either Coutinho staging 1 or 2, or polyneuropathy disability [PND] score ≤IIIb). Patients with more severe staging of ATTRv-PN were excluded. There is currently lack of sufficient evidence to support the safety and efficacy of eplontersen (Wainua) in patients with more severe forms of disease.

IX. Symptoms of ATTRv-PN commonly start with lower limb impairment, orthostatic hypotension, and gastrointestinal disturbances, but later lead to progressive muscle wasting, central nervous system dysfunction, renal impairment, and increasingly substantial functional impairment.

X. Studies suggest that orthotopic liver transplantation causes prompt replacement of variant transthyretin by the donor wild type in the plasma. The NEURO-TTRansform study excluded patients who had previously received a liver transplant or are anticipating liver transplant within one year of screening. There is currently insufficient evidence to evaluate the efficacy of eplontersen (Wainua) in treatment of patients who are refractory to or anticipating liver transplant. Phase 3 trials studying the safety and efficacy of TTR silencer therapy in this disease space also exclude patients with prior or anticipated liver transplant.

XI. The NEURO-TTRansform study excluded patients who had a New York Hearth Association (NYHA) functional classification score of ≥ III heart failure. There is currently insufficient evidence to support the efficacy and safety of eplontersen (Wainua) in the treatment of patients who have more severe cardiovascular disease. According to ACC 2023 guidelines, "…patients with advanced [cardiac disease], treatment aimed at TTR stabilization is unlikely to be of significant benefit.".

Investigational or Not Medically Necessary Uses

I. Eplontersen (Wainua) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Cardiac amyloidosis due to wild-type or mutant TTR

i. Eplontersen (Wainua) in the cardiac amyloidosis setting (sans polyneuropathy involvement) is currently under investigation in a Phase 3, multicenter, double-blinded study (CARDIO-TTRansform trial). It is currently in the active study phase, estimated to be completed in June of 2025.

B. Transthyretin amyloidosis of the wild-type origin (ATTRwt)
   i. Pivotal trials leading to FDA approval of eplontersen (Wainua) were specifically in the hereditary transthyretin-mediated amyloidosis setting. Wild-type TTR is not considered hereditary. There are currently no ongoing or active trials to study the use of eplontersen (Wainua) in the non-hereditary disease space. There is currently a lack of sufficient evidence or additional scientific literature to support the use of eplontersen (Wainua) for ATTRwt.

C. Pediatrics and adolescents under the age of 18 years old
   i. There are currently no ongoing or active trials to study the use of eplontersen (Wainua) in pediatric patients less than 18 years of age. There is currently a lack of sufficient evidence or additional scientific literature to support the use of eplontersen (Wainua) in members less than 18 years of age.

D. Use of eplontersen (Wainua) in combination with other TTR silencer therapy (i.e., inotersen (Tegsedi), patisiran (Onpattro), tafamidis meglumine (Vyndaqel)).
   i. There are currently no ongoing or active trials to study the use of eplontersen (Wainua) in combination with other TTR silencer therapy. There is currently a lack of additional scientific literature to support the use of eplontersen (Wainua) in combination with other TTR silencers.

References

1. Approved eplontersen (Wainua) Dossier. AstraZeneca. December, 2023.
2. WAINUA. Prescribing information. Astrazeneca Pharmaceuticals LP; 2023
3. Coelho, Teresa et al. “Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy.” JAMA vol. 330,15 (2023): 1448-1458.
4. Writing Committee et al. “2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis: A Report of the American College of Cardiology Solution Set Oversight Committee.” Journal of the American College of Cardiology vol. 81,11 (2023): 1076-1126. doi:10.1016/j.jacc.2022.11.022
5. Kittleson, Michelle M et al. “Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association.” Circulation vol. 142,1 (2020): e7-e22.
6. Adams, David et al. “Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy.” Journal of neurology vol. 268,6 (2021): 2109-2122. doi:10.1007/s00415-019-09688-0
7. Luigetti, Marco et al. “Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: Current Perspectives on Improving Patient Care.” Therapeutics and clinical risk management vol. 16 109-123. 21 Feb. 2020
8. Vélez-Santamaría, Valentina et al. “Hereditary Transthyretin Amyloidosis with Polyneuropathy: Monitoring and Management.” International journal of general medicine vol. 15 8677-8684. 20 Dec. 2022, doi:10.2147/IJGM.S338430

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
inotersen (TEGSEDI®)	Hereditary transthyretin-mediated amyloidosis with polyneuropathy

tafamidis meglumine (Vyndaqel®); tafamidis (Vyndamax™)	Cardiomyopathy of wide type (ATTRwt-CM); Hereditary transthyretin-mediated amyloidosis (hATTR-CM)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2024

erdafitinib (Balversa™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP031

Split Fill Management*

Description

Erdafitinib (Balversa) is an oral kinase inhibitor that inhibits enzymatic activity of FGFR 1-4.

Length of Authorization

- Initial: Three months, split fill
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*	DDID
erdafitinib (Balversa)	3 mg tablets	Advanced or metastatic urothelial carcinoma FGFR3 or FGFR2 genetic alteration, second-line after platinum therapy progression	**Maintenance**: 90 tablets/30 days	206400
	4 mg tablets		**Initial**: 28 tablets per 14-day supply for one fill **Maintenance**: 60 tablets/30 days	206401
	5 mg tablets		**Maintenance**: 30 tablets/30 days	206402

*Total daily dose should not exceed 9 mg per day. This may be achieved by 5 mg plus 4 mg, or by three 3mg tablets.

Initial Evaluation

I. Erdafitinib (Balversa) may be considered medically necessary when the following criteria 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 urologist; **AND**
   C. Not to be used in combination with other oncolytic medications (i.e., must be used as a monotherapy for the conditions listed below); **AND**
   D. The provider attests that the member will be treated with a maximum of 8 mg per day for at least two weeks to assess for tolerability before considering a total daily dose of 9 mg per day; **AND**
   E. A diagnosis of urothelial carcinoma when the following are met:
      1. Disease is considered advanced or metastatic; **AND**
      2. Genetic alteration is FGFR**3** point mutation or fusion as detected by an FDA-approved test; **AND (one of i or ii)**
         i. The member has previously progressed during or following at least one line of prior platinum-containing chemotherapy (e.g., cisplatin, carboplatin); **OR**

ii. The member previously progressed during or following neoadjuvant or adjuvant platinum-containing chemotherapy (e.g., cisplatin, carboplatin); **AND**
    a. The platinum-containing chemotherapy was administered within the last 12 months

II. Erdafitinib (Balversa) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Urothelial carcinoma that has FGFR**2** genetic alteration (e.g., fusion or point mutation)

III. Erdafitinib (Balversa) is considered investigational when used for all other conditions, including, but not limited to:
    A. Urothelial carcinoma prior to the advanced or metastatic setting
    B. Urothelial carcinoma without FGFR mutation, or without previous treatment with platinum-based chemotherapy
    C. For urothelial carcinoma, or otherwise, treatment with a dose greater than 9 mg per day
    D. Conditions outside of urothelial carcinoma (e.g., Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.)

Renewal Evaluation

I. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
II. The medication is not used in combination with other oncolytic medications (i.e., erdafitinib [Balversa] is used as monotherapy); **AND**
III. Tumor response is documented with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
IV. The member has an absence of unacceptable toxicity from the drug (e.g., ophthalmic disturbances, hyperphosphatemia).

Supporting Evidence

I. Erdafitinib (Balversa) was evaluated in one, single-arm, open-label trial. Eighty-seven subjects (n=87) had advanced or metastatic urothelial carcinoma with FGFR**2** or FGFR**3** genetic alterations. Additionally, subjects must have progressed on or after at least one line of prior platinum-containing chemotherapy. This included those that had received neoadjuvant or adjuvant platinum-containing chemotherapy in the past 12 months.
II. No pediatric patients were included in the trial. Subjects assessed were between the ages of 36 and 87. Ninety-seven percent of subjects had received prior cisplatin or carboplatin, and 10% had received both. Twenty-four percent of subjects had received prior anti-PD-L1/PD-1 therapy (immunotherapy). No concomitant oncolytic medications were allowed during the trial.
III. The study assessed for objective response rate (ORR), including both partial and complete response (PR and CR), and duration of response (DoR). Thirty-two percent of subjects met the ORR (2 patients showed CR), and the median duration of response was 5.4 months.
IV. High rates of dose-reduction and dose-interruption were observed, at 53% and 68% respectively. Serious adverse events including, but not limited to, ophthalmic disturbances, hyperphosphatemia, and fatal myocardial infarction, occurred during the trial (1-20%).

Investigational or Not Medically Necessary Uses

I. The pivotal trial evaluated for the FDA-approved indication of urothelial carcinoma included six patients with a FGFR**2** fusion genetic alteration, and no patients that had FGFR**2** point mutation. None of these six patients showed an ORR on or after treatment with erdafitinib (Balversa). As of April 2019, there is no evidence that this population has responded to therapy.
II. Currently, the available outcomes data for erdafitinib (Balversa) was based on a maximum dose of 9 mg per day. No subjects were on concurrent oncolytic therapies. All subjects were verified to be with FGFR-mutation, and with advanced or metastatic urothelial carcinoma. Safety and efficacy outcomes in patients not previously progressed on or after platinum-containing chemotherapy is unknown at the time of this writing.
III. Erdafitinib (Balversa) is currently in clinical trials for a variety of other conditions (e.g, Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.).

*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. Balversa {Prescribing Information]. Janssen Pharmaceutical Companies: Horsham, PA. April 2019.
2. National Comprehensive Cancer Network. NCCN Guidelines: Bladder Cancer V3.2019. Available at https://www.nccn.org/professionals/physician_gls/default.aspx. Updated April 23, 2019. Accessed April 29, 2019.
3. UpToDate. Overview of the initial approach and management of urothelial bladder cancer. Lerner S.P., Raghavan D. March 2019. Available at: https://www.uptodate.com/contents/overview-of-the-initial-approach-and-management-of-urothelial-bladder-cancer?search=urothelial%20carcinoma&source=search_result&selectedTitle=1~82&usage_type=default&display_rank=1. Accessed April 29, 2019.
4. FDA News Release. FDA approved first targeted therapy for metastatic bladder cancer. April 12, 2019. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-metastatic-bladder-cancer. Accessed on April 29, 2019.
5. U.S. National Library of Medicine Clinical Trials. An efficacy and safety study of JNJ-42756493 in participants with urothelial cancer. Clinicaltrials.gov. Last updated March 29, 2019. Available at: https://clinicaltrials.gov/ct2/show/NCT02365597. Accessed on April 29, 2019.

Policy Implementation/Update:

Date Created	April 2019
Date Effective	August 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**

esketamine (Spravato™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP026

Description

Esketamine (Spravato) is an intranasal N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism by which esketamine (Spravato) exerts its antidepressant effect is unknown.

Length of Authorization

- Treatment resistant depression (TRD)
  - Initial: Six months
  - Renewal: 12 months
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior
  - Initial: Four weeks
  - Renewal: Cannot be renewed

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit*
esketamine (Spravato)	Treatment resistant depression (TRD), as monotherapy or in conjunction with an oral antidepressant	56 mg dose kit	**Initial:** • PA #1: 24 devices per 28 days • PA #2 (maintenance dosing): 12 devices per 28 days* for the remaining five months **Renewal:** 12 devices per 28 days*
		84 mg dose kit	
	Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior, in conjunction with an oral antidepressant	56 mg dose kit	24 devices per 28 days
		84 mg dose kit	

*Allows for 56mg or 84mg at weekly or every other week dosing.

Initial Evaluation

I. **Esketamine (Spravato)** may be considered medically necessary when the following criteria below are met:
   A. Member is between 18 and 64 years of age; **AND**
   B. Medication is prescribed by, or in consultation with, a psychiatrist; **AND**
   C. Member does **not** have a current or prior Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of:
      1. Concomitant psychotic disorder; **OR**
      2. Major depressive disorder (MDD) with psychosis; **OR**
      3. Bipolar or related disorders (confirmed by the MINI); **OR**

4. Obsessive compulsive disorder (current episode only); **OR**
5. Intellectual disability; **OR**
6. Personality disorder; **AND**

D. The member does **not** have a contraindication to and has **not** previously failed ketamine; **AND**

E. A diagnosis of **Treatment Resistant Depression (TRD)** when the following are met:
   1. Diagnosis of **Major Depressive Disorder (MDD)** was made following Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria; **AND**
      i. Member is experiencing a persistent MDD episode, the duration of which must be greater than, or equal to, two years; **OR**
      ii. Member is experiencing recurrent MDD (an interval of at least two consecutive months between separate episodes during which criteria are not met for a major depressive episode); **AND**
   2. Documentation of baseline assessment [e.g. Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAM-D), Nine-Item Patient Health Questionnaire (PHQ-9), Sheehan Disability Scale (SDS)]; **AND**
   3. Treatment with **ALL** of the following has been ineffective, contraindicated, or not tolerated in the treatment of the current episode:
      i. Psychotherapy in conjunction with antidepressant treatment [e.g. cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), problem-solving therapy (PST) etc.]; **AND**
      ii. At least ~~four~~ three antidepressants from two or more different classes (i.e. SSRI, SNRI, TCA, MAO) at an optimized dose for at least 8 weeks; **AND**
      iii. Augmentation with an atypical antipsychotic (i.e. olanzapine, aripiprazole), lithium, or liothyronine; **OR**

F. A diagnosis of **depressive symptoms with major depressive disorder (MDD) with acute suicidal ideation or behavior** when the following are met:
   1. Member has a severe depressive episode (cannot care for self, participate in life, has persistent thoughts of hopelessness, persistent sad, anxious or "empty" mood, thoughts of suicide); **AND**
   2. Provider attests that without esketamine (Spravato), member may require an emergency department (ED) visit or an inpatient psychiatric hospitalization in the next 24-48 hours; **AND**
   3. Documentation of ongoing use of an antidepressant to be used concurrently with esketamine (Spravato)

II. Esketamine (Spravato) is considered not medically necessary when criteria above are not met and/or when used for treatment resistant depression in members 65 years of age or older.

III. Esketamine (Spravato) is considered investigational when used for all other conditions, including but not limited to:
   A. Pain management
   B. Anesthesia

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. Documentation of improvement from baseline assessment (e.g., PHQ-9, Clinically Useful Depression Outcome Scale, Quick Inventory of Depressive Symptomatology-Self Report 16 Item, MADRS, HAM-D) by 50% or more, indicating clinical benefit for treatment resistant depression; **OR**
    A. Documentation attesting member is in remission (MADRS total score ≤12, HRSD or HAM-D score less than 10, PHQ-9 score less than 5 or SDS score of less than 6 at day 28,); **AND**
IV. Provider attests that member is utilizing the least frequent dosing to maintain disease response and/or remission

Supporting Evidence

I. Age requirements for treatment with esketamine (Spravato) are on made on the basis of clinical trial requirements. Clinical trials showing statistical significance in clinical outcomes had a population aged between 18-64 years of age. TRANSFORM-3 evaluated patients 65 years and older and outcomes were found to be not statistically significant. TRANSFORM-1 evaluated a similar population to pivotal trial TRANSFORM-2 but found a lack of statistical significance in clinical outcomes in patients aged 18-64 years.
II. Considering the severity and complexity of the disease state and the safety profile of esketamine (Spravato), therapy is required to be prescribed by, or in consultation with, a psychiatrist.
III. Patients with DSM-5 diagnosis of concomitant psychotic disorder, MDD with psychosis, bipolar or related disorders, obsessive compulsive disorder (OCD), and personality disorder were excluded from the esketamine (Spravato) landmark studies (NCT02418585 and NCT02493868) as well as the monotherapy trials (NCT04599855) and are not currently being studied for treatment with esketamine (Spravato). The known adverse events include dissociative or perceptual changes (including distortion of time, space, and illusions) and derealization and depersonalization (61% to 75% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale). There is no safety and efficacy clinical trial data to support the use of esketamine (Spravato) in this patient population. Considering the symptomology of the disease states, known adverse events and unknown long-term safety profile, it is unknown how esketamine (Spravato) would affect this patient population.
IV. There is no clinical trial data to show efficacy of esketamine (Spravato) in patients who have not responded to ketamine infusions that have been used in treatment of MDD off label. There is no clinical trial safety data to support the use of esketamine (Spravato) if ketamine has been contraindicated or not tolerated. Participants who have previously demonstrated nonresponse of depressive symptoms to ketamine were excluded from the clinical trial.
V. Initial clinical trials were conducted as dual therapy in conjunction with oral antidepressants and esketamine (Spravato) is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults and depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. Later clinical trials assessed the efficacy of esketamine (Spravato) as monotherapy for the treatment of TRD only.

VI. Esketamine (Spravato) is indicated for use in conjunction with an oral antidepressant or as monotherapy for the treatment of treatment-resistant depression (TRD) in adults. In clinical trials, TRD was defined as a DSM-5 diagnosis of major depressive disorder (MDD) [recurrent or single-episode (duration ≥2 years) without psychotic features or recurrent MDD (an interval of at least two consecutive months between separate episodes during which criteria are not met for a major depressive episode);] in patients who have not responded adequately to at least two different antidepressants of adequate dose and duration in the current depressive episode.

VII. There are no current American Psychiatric Association (APA) guidelines specific to TRD. In the 2019 APA guidelines for treatment of depression in the general adult population, initial treatment of MDD was recommended to include a second-generation oral antidepressant and psychotherapy, either as monotherapy or in combination with each other.

- Recommended psychotherapies include:
  - Behavioral therapy
  - Cognitive-behavioral therapy (CBT) evaluates, challenges, and modifies dysfunctional thoughts that maintain depression. Behavioral strategies are also used to increase pleasant activities to treat anhedonia.
  - Interpersonal psychotherapy (IPT) is a structured and brief intervention addressing social issues that maintain depression.
  - Problem-solving therapy (PST) teaches to define personal problems, develop multiple solutions, identify the best one and implement it, then assess its effectiveness.
  - Supportive therapy
- Meta-analyses that compare the effectiveness of CBT, IPT, and PST indicate no large differences in effectiveness between these treatments.

VIII. Standard practice for treatment resistant depression, supported by the American Psychiatric Association (APA), include:

- Use of monotherapy antidepressants
- Trial of more than one antidepressant
- Augmentation with additional antidepressant therapy
- Augmentation with other therapies including antipsychotics, liothyronine, or lithium.

IX. The National Institute for Health and Care Excellence (NICE) guideline for treatment of depression defines treatment resistant depression (TRD) as 'people with major depressive disorder who fail to respond to two different oral antidepressants'. Within the recommended treatment pathway, treatment options for TRD include:

- Oral antidepressants
- Augmentation with lithium or an antipsychotic treatment, or combined with another oral antidepressant
- Electroconvulsive therapy (ECT)

X. For the treatment of depressive symptoms with major depressive disorder (MDD) with acute suicidal ideation or behavior, esketamine (Spravato) was studied in 456 patients in two phase III, double-blind, randomized, multicenter studies (ASPIRE I and ASPIRE II). Esketamine was compared to placebo with standard-of-care (SOC).

- The first dose of study drug was administered in an emergency department or in an inpatient psychiatric unit. Patients were to remain hospitalized for a recommended 5 days (14 days in 7 countries in European Union based on health authority request during the clinical trial approval). Shorter or longer periods of hospitalization were permitted, if clinically necessary, per local standard practice.

- The primary outcome: Change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline (day 1, pre-dose) to 24 hours post–first dose
    - ASPIRE I: esketamine + SOC (mean [SD]: –16.4 [11.95]) and placebo + SOC (–12.8 [10.73]), with significantly greater improvement with esketamine (least-squares mean difference [SE]: –3.8 [1.39]; 95% CI, −6.56 to −1.09; 2-sided P = 0.006)
    - ASPIRE II: esketamine + SOC (mean [SD]: –15.7 [11.56]) and the placebo + SOC (–12.4 [10.43]), with significantly greater improvement in depressive symptoms with esketamine ([SE]: –3.9 [1.39], 95% CI: -6.60, -1.11; 2-sided p=0.006).
- The secondary: Change in the Clinical Global Impression - Severity of Suicidality - Revised (CGI-SS-R) score from baseline to 24 hours after the first dose
    - ASPIRE I and ASPIRE II: Both treatment groups demonstrated improvements in severity of suicidality scores; however, the treatment difference was not significant (P=0.379)
    - The efficacy of esketamine (Spravato) regarding suicidality has not been established in the clinical trial.

XI. Suicidal ideation is defined as thoughts of serving as the agent of one's own death and may vary in seriousness depending on the specificity of suicide plans and the degree of suicidal intent.
- Suicidal intent is the subjective expectation and desire for a self-destructive act to end in death.
- Lethality of suicidal behavior is the objective danger to life associated with a suicide method or action. Lethality is distinct from and may not always coincide with an individual's expectation of what is medically dangerous.

XII. Symptoms for MDD, according to Anxiety and Depression Association of America (ADAA), are persistent sad, anxious or "empty" mood, feelings of hopelessness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest or pleasure in hobbies and activities, including sex, decreased energy, fatigue, feeling "slowed down", difficulty concentrating, remembering, making decisions, insomnia, early-morning awakening, or oversleeping, low appetite and weight loss or overeating and weight gain, thoughts of death or suicide, suicide attempts, restlessness, irritability, and persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders and pain for which no other cause can be diagnosed.

XIII. In ASPIRE I and ASPIRE II clinical trial the safety and efficacy of esketamine (Spravato) has been evaluated in the treatment of patients for whom acute psychiatric hospitalization (within 24 to 48 hours) is clinically warranted due to their imminent risk of suicide.

XIV. The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items (to evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel [interest level], pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), summed for a total possible score range of 0-60. Higher scores represent a more severe condition. Negative change in score indicates improvement. MADRS measures severity of depression in individuals 18 years and older. Each item is rated on a 7-point scale. The scale is an adaptation of the Hamilton Depression Rating Scale and has a greater sensitivity to change over time. The scale can be completed in 20 to 30 minutes.

XV. The Patient Health Questionnaire (PHQ) is a self-report measure designed to screen depressive symptoms. It takes one to five minutes to complete and roughly the same amount of time for a clinician to review the responses. The PHQ-9 is available in multiple languages. The diagnostic validity of the PHQ has recently been established in 2 studies involving 3,000 patients in 8 primary care clinics and 3,000 patients in 7 obstetrics-gynecology clinics. At 9 items, the PHQ

depression scale (which we call the PHQ-9) is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based.

XVI. The Hamilton Rating Scale for Depression, abbreviated HDRS, HRSD, or HAM-D, measures depression in individuals before, during, and after treatment. The scale is administered by a health care professional and contains 21 items, but is scored based on the first 17 items, which are measured either on 5-point or 3-point scales. It takes 15 to 20 minutes to complete and score. Results of a meta-analysis over a period of 49 years suggest that HRSD provides a reliable assessment of depression.

XVII. The SDS is a brief, 5-item self-report tool that assesses functional impairment in work/school, social life, and family life. Total score ranges from 0-30 (0 unimpaired, 30 highly impaired) and segments [work/school (0-10), social life (0-10), family life/home responsibilities (0-10] get scored. Scores of ≥5 on any of the 3 scales, with high scores associated with significant functional impairment, and sensitivity is 83% and specificity 69%.

XVIII. Remission for MADRS is defined with a total score ≤12, HRSD or HAM-D score less than 10, PHQ-9 score less than 5 or SDS score of less than 6 at day 28.

XIX. Data from SUSTAIN-2, a phase 3, open-label, long term (up to one year) clinical trial to evaluate long-term safety and efficacy of esketamine nasal spray plus oral antidepressant therapy, showed that reduction in dosing frequency from weekly to every-other-week regimens was achieved in 38.1% of patients. This indicates that for a considerable majority of patients, dose reduction to every-other-week regimens may not be clinically appropriate. Provider evaluation of the member's likelihood to maintain clinical stability or remission of depressive symptoms on weekly vs. every-other-week dosing can be reliably trusted with minimal risk for overutilization.

Investigational or Not Medically Necessary Uses

I. Pain management
   A. Not FDA approved. Safety and efficacy for use of esketamine (Spravato) for pain management or anesthesia has not been established.

Appendix

I. Table 1: Quantity limits on per week level for the treatment of treatment resistant depression (TRD)

	QL	Dosing Schedule		Cumulative Spravato Doses/Devices
Induction Phase: Week 1 - 4	24 devices/28 days*	Week 1 (twice weekly dosing)	Day 1, dose 1	56 mg (2 devices)
			Second dose	56 mg (4 devices) or 84 mg (5 devices)
		Week 2 (twice weekly dosing)		56 mg (8 devices) or 84 mg (11 devices)
		Week 3 (twice weekly dosing)		56 mg (12 devices) or 84 mg (17 devices)
		Week 4 (twice weekly dosing)		56 mg (16 devices) or 84 mg (23 devices)
Maintenance Phase: Week 5 - 8	12 devices/28 days	Week 5 (once a week dosing)		56 mg (2 devices) or 84 mg (3 devices)
		Week 6 (once a week dosing)		56 mg (4 devices) or 84 mg (6 devices)
		Week 7 (once a week dosing)		56 mg (6 devices) or 84 mg (9 devices)
		Week 8 (once a week dosing)		56 mg (8 devices) or 84 mg (12 devices)
Maintenance: Week 9 and after	12 devices/28 days	Week 9 - ∞ (every two weeks dosing or once weekly dosing)		56 mg (4-8 devices/28) or 84 mg (6 – 12 devices/28)

*Max allowance: 24 devices/28 days: This includes the 2 devices from the 56mg dose done on day one. Although we technically expect patients to use a maximum of 23 devices, a maximum of 24 devices in the first month would allow all weeks to pay below the max dose loaded.

II. Table 1: Quantity limits on per week level for the treatment of treatment resistant depression (TRD)

III. Table 2: Antidepressant Example (*please note list below is not comprehensive*)

Selective Serotonin Reuptake Inhibitors (SSRI)	
• Paroxetine (Paxil) • Fluvoxamine (Luvox) • Escitalopram (Lexapro)	• Sertraline (Zoloft) • Fluoxetine (Prozac) • Citalopram (Celexa)
Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	
• Duloxetine (Cymbalta) • Venlafaxine (Effexor) • Desvenlafaxine (Pristiq)	• Milnacipran (Savella) • Levomilnacipran (Fetzima)
Tricyclic antidepressant (TCA)	
• Amitriptyline (Elavil) • Clomipramine (Anafranil) • Nortriptyline (Pamelor)	
Other	
• Bupropion (Wellbutrin) • Mirtazapine (Remeron)	• Vilazodone (Viibryd) • Vortioxetine (Trintellix) • Nefazodone (Serzone)

III. Table 3: Quantity limits for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Week	**Cumulative Spravato Doses/Devices**	**Billing Units**
Week 1 (twice weekly)	84mg (6 devices)	Billed under S code: 672 units (to allow for 56mg or 84mg) Billed under G code: 8 units (to allow for 56mg or 84mg)
Week 2 (twice weekly)	56mg (4 devices) or 84mg (12 devices)	
Week 3 (twice weekly)	56mg (8 devices) or 84mg (18 devices)	
Week 4 (twice weekly)	56mg (10 devices) or 84mg (24 devices)	

IV. Table 4: Medical billing units

	Stage:	**Total Units Approved:**		**Length of Approval:**
		S Code	**G Code**	
TRD	Initial	2352	28	6 months
	Continuation/Renewal	4368	56	12 months
MDD with acute suicidal ideation or behavior	Initial	672	8 units	4 weeks
	Continuation/Renewal	N/A	N/A	N/A
S0013 = Units: 1:1 conversion (1 unit = 1mg)				
G2082 [56mg] = Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care provider and provision of up to 56 mg of esketamine nasal self-administration, includes 2 hours post-administration observation				

G2083 [84mg] = Office or other outpatient visit for the evaluation and management of an established patient that requires the supervision of a physician or other qualified health care provider and provision of greater than 56 mg of esketamine nasal self-administration, includes 2 hours post-administration observation.



	Quantity Limit	Dosing Schedule		Cumulative Spravato Doses/ Devices	Billing Units
Induction Phase: Week 1 - 4	24 devices/28 days*	Week 1 (twice weekly dosing)	Day 1, dose 1	56 mg (2 devices)	Billed under S code: 644 units (to allow for 56mg or 84mg) Billed under G code: 8 units (to allow for 56mg or 84mg)
			Second dose	56 mg (4 devices) or 84 mg (5 devices)	
		Week 2 (twice weekly dosing)		56 mg (8 devices) or 84 mg (11 devices)	
		Week 3 (twice weekly dosing)		56 mg (12 devices) or 84 mg (17 devices)	
		Week 4 (twice weekly dosing)		56 mg (16 devices) or 84 mg (23 devices)	
Maintenance Phase: Week 5 - 8	12 devices/28 days	Week 5 (once a week dosing)		56 mg (2 devices) or 84 mg (3 devices)	Billed under S code: 336 units (to allow for 56mg or 84mg units) Billed under G code: 4 units (to allow for 56mg or 84mg units)
		Week 6 (once a week dosing)		56 mg (4 devices) or 84 mg (6 devices)	
		Week 7 (once a week dosing)		56 mg (6 devices) or 84 mg (9 devices)	
		Week 8 (once a week dosing)		56 mg (8 devices) or 84 mg (12 devices)	
Maintenance: Week 9 and after	12 devices/28 days	Week 9 - ∞ (every two weeks dosing or once weekly dosing)		56 mg (4-8 devices/28) or 84 mg (6 – 12 devices/28)	Billed under S code: 336 units (to allow for 56mg or 84mg units) Billed under G code: 4 units (to allow for 56mg or 84mg units)
Units: 1:1 conversion (1 unit = 1mg)					

For further guidance, please reference Spravato's billing guide at: https://www.spravatohcp.com/sites/www.spravatohcp-v1.com/files/spravato_access_reimbursement_guideline.pdf?v=14878

References

1. Spravato [Prescribing Information]. Janssen Pharmaceuticals Inc.: Titusville, NJ. January 2025.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps; a STAR*D report. Am J Psychiatry. 2006;163:1905-1917.
3. Popova V, Daly EJ, Trivedi M, Cooper K, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. Am J Psychiatry. 2019 Jun 1;176(6):428-438. doi: 10.1176/appi.ajp.2019.19020172. Epub 2019 May 21.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ArrayRx administered by moda HEALTH

4. Daly EJ, Trivedi MH, Janik A, Li H, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2019 Jun 5. doi:10.1001/jamapsychiatry.2019.1189.
5. Alan J. Gelenberg, M.D., Marlene P. Freeman, M.D., et al. PRACTICE GUIDELINE FOR THE Treatment of Patients With Major Depressive Disorder. AMERICAN PSYCHIATRIC ASSOCIATION. 2010. Third edition
6. Thase M, Connolly KR. Unipolar treatment resistant depression in adults: Epidemiology, risk factors, assessment, and prognosis. In: UpToDate. Roy-Byrne P, Solomon D (Ed). Waltham, MA 2019.
7. Crowell AL, Riva-Posse, Holtzheimer PE, et al. Long-term outcomes of subcallosal cingulate deep brain stimulation for treatment-resistant depression [published online Oct 4, 2019]. Am J Psychiatry. doi:10.1176/appi.ajp.2019.18121427
8. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 2007; 62:1208–1216
9. Qaseem, A., Barry, M. J., & Kansagara, D. Nonpharmacologic Versus Pharmacologic Treatment of Adult Patients With Major Depressive Disorder: A Clinical Practice Guideline From the American College of Physicians. 2016, March 1. Retrieved from https://annals.org/aim/fullarticle/2490527/nonpharmacologic-versus-pharmacologic-treatment-adult-patients-major-depressive-disorder-clinical
10. Fu DJ, Ionescu DF, Li X, et al. Esketamine Nasal Spray for Rapid Reduction of Major Depressive Disorder Symptoms in Patients Who Have Active Suicidal Ideation With Intent: Double-Blind, Randomized Study (ASPIRE I). J Clin Psychiatry. 2020;81(3):19m13191. Published 2020 May 12. doi:10.4088/JCP.19m13191
11. Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II) [published online ahead of print, 2020 Aug 29]. Int J Neuropsychopharmacol. 2020;pyaa068. doi:10.1093/ijnp/pyaa068
12. American Psychiatric Association: Practice Guideline for the Assessment and Treatment of Patients With Suicidal Behaviors. Am J Psychiatry 2003; 160(Nov suppl):1–60 [G]
13. Anxiety and Depression Association of America (ADAA). Symptoms. Retrieved from https://adaa.org/understanding-anxiety/depression/symptoms
14. Fantino, B., & Moore, N. (2009). The self-reported Montgomery-Asberg Depression Rating Scale is a useful evaluative tool in Major Depressive Disorder. BMC psychiatry, 9, 26. https://doi.org/10.1186/1471-244X-9-26
15. Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. Journal of general internal medicine, 16(9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x
16. Martin, A., Rief, W., Klaiberg, A., & Braehler, E. (2006). Validity of the brief patient health questionnaire mood scale (PHQ-9) in the general population. General Hospital Psychiatry, 28(1), 71-77. https://doi.org/10.1016/j.genhosppsych.2005.07.003
17. Trajković, G., Starčević, V., Latas, M., Leštarević, M., Ille, T., Bukumirić, Z., & Marinković, J. (2011). Reliability of the Hamilton Rating Scale for Depression: A meta-analysis over a period of 49 years. Psychiatry Research, 189(1), 1-9. http://dx.doi.org/10.1016/j.psychres.2010.12.007
18. Rush JA, et al. Handbook of Psychiatric Measures, 2000 American Psychiatric Association, 113-115
19. Canuso CM, Singh JB, Fedgchin M, Alphs L, Lane R, Lim P, Pinter C, Hough D, Sanacora G, Manji H, Drevets WC. Efficacy and Safety of Intranasal Esketamine for the Rapid Reduction of Symptoms of Depression and Suicidality in Patients at Imminent Risk for Suicide: Results of a Double-Blind, Randomized, Placebo-Controlled Study. Am J Psychiatry. 2018 Jul 1;175(7):620-630. doi: 10.1176/appi.ajp.2018.17060720. Epub 2018 Apr 16.
20. Wajs E, Aluisio L, Holder R, et al. Esketamine nasal spray plus oral antidepressant in patients with treatment-resistant depression: assessment of long-term safety in a Phase 3, open-label study (SUSTAIN-2). J Clin Psychiatry 2020;81(3):19m12891.
21. Bennabi D, Charpeaud T, Yrondi A, et al. Clinical guidelsin for the management of treatment-resistant depression: French recommendations from experts, the French Association for Biologic Psychiatry and Neuropsychopharmacology and the foundation FondaMental. BMC Psychiatry. 2019; 19:262.
22. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from https://www.apa.org/depression-guideline.
23. National Institute of Health and Care. Depression in adults: recognition and management Clinical Guideline. 2009.
24. U.S. Food and Drug Administration. Repetitive Trascranial Magentic Stimulation (rTMS) Systems – Class II Special Controls Guidance for Industry and FDA Staff. Updated as of 3/23/2018. Accessed from:

https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/repetitive-transcranial-magnetic-stimulation-rtms-systems-class-ii-special-controls-guidance#11.
25. U.S. Food and Drug Administration. Electroconvulsive Therapy (ECT) Devices for Class II Intended Uses – Draft Guidance for Industry, Clinicians and Drug Administration Staff. Issued 12/29/2015. Accessed from: https://www.fdanews.com/ext/resources/files/2016/01/01-16-FDA-ECT.pdf?1451949526
26. Janik A, Qiu X, Lane R, Popova V, Drevets WC, Canuso CM, Macaluso M, Mattingly GW, Shelton RC, Zajecka JM, Fu DJ. Esketamine Monotherapy in Adults With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry. 2025 Jul 2:e251317

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy criteria to remove requirement for combination oral antidepressant (OAD) use in the treatment of TRD, reduced the number of OAD trials required, added liothyronine as an augmentation therapy, removed criteria requiring rTMS/ECT, updated billing units calculation.	10/2025
Extended initial duration approval timeframe from two months to six months	08/2023
Added medical billing unit conversion	06/2023
Updated QL table/PAC instructions, appendix tables, and references	04/2023
• Removed requirement of augmentation with an additional antidepressant • Updated renewal requirement for weekly dosing to require provider attestation that member is using least frequent dosing possible to maintain symptom control/remission • Updated quantity limit to 12 devices per month to align with allowance of weekly administration; noted quantity exceptions will not be allowed in the maintenance phase • Updated supporting evidence	05/2022
• Added new indication of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior and appropriate criteria • Updated criteria for TRD to reflect that prior treatment failures must be associated with the current depressive episode and changed the number of prior antidepressants to four from two different classes	10/2020
• Added major depressive disorder (MDD) symptoms, including suicidal ideation in patients who are at imminent risk for suicide as an investigational indication • Added criteria: ○ Documentation of improvement from baseline assessment by 50% or more, indicating clinical benefit for treatment resistant depression or documentation attesting member is in remission (MADRS total score ≤12, HRSD or HAM-D score less than 10, PHQ-9 score less than 5 or SDS score of less than 6 at day 28,); ○ The member does not have a contraindication to and has not previously failed ketamine ○ Treatment has been ineffective, contraindicated, or not tolerated with psychotherapy in conjunction with antidepressant treatment [e.g. cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), problem-solving therapy (PST) etc.] and ECT (Electroconvulsive therapy) or repetitive transcranial magnetic stimulation (rTMS) unless all are contraindicated has been ineffective, contraindicated, or not tolerated ○ Diagnoses of major depressive disorder (MDD) was made following Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria and member is experiencing a persistent MDD episode (duration greater than or equal to two years) or member is experiencing recurrent MDD (an interval of at least two consecutive months between separate episodes during which criteria are not met for a major depressive episode) ○ Member doesn't have a current or prior Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of concomitant psychotic disorder or major depressive disorder (MDD) with psychosis or bipolar or related disorders (confirmed by the MINI) or obsessive-compulsive disorder (current episode only) or intellectual disability or personality disorder ○ Medication is prescribed by, or in consultation with a psychiatrist • Updated quantity limit to better align with dosing regimen	03/2020
Policy effective	05/2019
Policy created	03/2019

estradiol/progesterone (Bijuva™)

UMP POLICY

Policy Type: Step Pharmacy Coverage Policy: UMP319

Description

Estradiol and progesterone (Bijuva) is an orally administered estrogen/progestin hormone replacement combination.

Length of Authorization

- Initial/Renewal: 12 months

Coverage Criteria

I. Estradiol and progesterone (Bijuva) may be considered medically necessary when the following criteria below are met:
   A. Treatment with two of the following: Amabelz, estradiol/norrthindone acet, Fyavolv, Jinteli, Lopreeza, Mimvey, Mimivey Lo, or norethindrone ac-eth estradiol has been ineffective, contraindicated, or not tolerated.

Policy Type: PA/SP Pharmacy Coverage Policy: UMP125

Split Fill Management*

Description

Everolimus (Afinitor, Afinitor Disperz) is an orally administered mammalian target of rapamycin (mTOR) inhibitor to reduce cell proliferation, angiogenesis, and glucose uptake.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
everolimus (generic Afinitor)	2.5 mg tablet	Angiomyolipoma of the kidney, tuberous sclerosis syndrome; Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole; Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic; Renal cell carcinoma, advanced disease; Subependymal giant cell astrocytoma	28 tablets/28 days For subependymal giant cell astrocytoma: quantity associated with 4.5 mg/m^2 daily
	5 mg tablet		
	7.5 mg tablet		
	10 mg tablet		
everolimus (Afinitor)	2.5 mg tablet		
	5 mg tablet		
	7.5 mg tablet		
	10 mg tablet		
everolimus (Afinitor Disperz)	2 mg tablet	Partial seizure, adjunct, tuberous sclerosis syndrome; Subependymal giant cell astrocytoma	Quantity associated with 5 mg/m^2 daily for partial seizure, 4.5 mg/m^2 daily for subependymal giant cell astrocytoma.
	3 mg tablet		
	5 mg tablet		
everolimus (generic Afinitor Disperz)	2 mg tablet		
	3 mg tablet		
	5 mg tablet		

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Initial Evaluation

I. **Everolimus (Afinitor Disperz)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, or neurologist; **AND**
   B. Generic everolimus (generic for Afinitor Disperz) is prescribed, unless member has a contraindication to generic product; **AND**
   C. A diagnosis of one of the following:
      1. **Subependymal giant cell astrocytoma; AND**
         i. Everolimus will not be used in combination with any other oncolytic medication; **OR**
      2. **Partial seizure, associated with tuberous sclerosis syndrome; AND**
         i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
         ii. The member is refractory to at least two other antiepileptic therapies (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**
         iii. The member will continue therapy with at least one other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine)

II. **Everolimus (Afinitor)** 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, hematologist, or neurologist; **AND**
   C. Generic everolimus (generic for Afinitor) is prescribed, unless member has a contraindication to generic product; **AND**
   D. A diagnosis of one of the following:
      1. **Angiomyolipoma of the kidney, associated with tuberous sclerosis; AND**
         i. The member does not require immediate surgery; **AND**
         ii. Everolimus will not be used in combination with any other oncolytic medication; **AND**
      2. **Breast cancer; AND**
         i. The member is a post-menopausal woman; **AND**
         ii. The member has advanced or metastatic disease (Stage III or IV); **AND**
         iii. Disease is confirmed as hormone receptor positive (HR+) and HER2-negative; **AND**
         iv. The member has failed a non-steroidal aromatase inhibitor [e.g., letrozole (Femara), anastrozole (Arimidex)]; **AND**
         v. Everolimus will be used in combination with exemestane (Aromasin); **OR**
      3. **Neuroendocrine tumor; AND**
         i. Everolimus will not be used in combination with any other oncolytic medication; **AND**

ii. The disease is progressive; **AND**
    a. Is of pancreatic origin; **OR**
    b. Is of gastrointestinal or lung origin and disease is well-differentiated, non-functional, unresectable and locally advanced, or metastatic; **OR**

4. **Renal cell carcinoma; AND**
    i. The member has advanced or metastatic (Stage III or IV) disease; **AND**
    ii. The member has tried and failed <u>one</u> anti-angiogenic therapy (e.g. pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], axitinib [Inlyta]); **AND**
    iii. Everolimus will be used as monotherapy **<u>OR</u>** in combination with lenvatinib (Lenvima); **OR**
5. **Subependymal giant cell astrocytoma; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication

III. Everolimus (Afinitor) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
    A. Carcinoid tumor

IV. Everolimus (Afinitor, Afinitor Disperz) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
    A. Graft-versus-host disease
    B. Ependymoma
    C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma
    D. Central nervous system cancers
    E. Kaposi's sarcoma
    F. Thymoma and thymic carcinoma
    G. Endometrial, ovarian, uterine cancers
    H. Prostate cancer
    I. Gastroesophageal carcinomas
    J. Waldenstrom macroglobulinemia

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. **Request is for everolimus (Afinitor Disperz); AND**
    A. Generic everolimus (generic for Afinitor Disperz) is prescribed, unless member has a contraindication to generic product; **AND**
    B. A diagnosis of one of the following:

1. **Subependymal giant cell astrocytoma**; **AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
2. **Partial seizure, associated with tuberous sclerosis syndrome; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in seizure frequency]; **AND**
    iii. The member will continue therapy with at least one other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **OR**

IV. **Request is for everolimus (Afinitor); AND**

A. Generic everolimus (generic for Afinitor) is prescribed, unless member has a contraindication to generic product; **AND**

B. A diagnosis of one of the following:

1. **Angiomyolipoma of the kidney, associated with tuberous sclerosis; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion]; **OR**
2. **Breast cancer; AND**
    i. Everolimus will be used in combination with exemestane (Aromasin); **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
3. **Neuroendocrine tumor; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
4. **Renal cell carcinoma; AND**
    i. Everolimus will be used as monotherapy; **OR** in combination with lenvatinib (Lenvima); **OR**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
5. **Subependymal giant cell astrocytoma; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size

Supporting Evidence

I. Everolimus (Afinitor, Afinitor Disperz) has been evaluated in many clinical studies for various indications; however, they were focused on oncological indications (and not for transplantation management and rejection prophylaxis). Of note, everolimus (Zortress) does not have a prior authorization and is indicated for transplantation management and rejection prophylaxis. Everolimus products (Afinitor, Afinitor Disperz, Zortress) are not interchangeable, and it is recommended that utilization stay within the products' FDA-approved indication(s). Given the much lower cost as well as timely need for transplant medication access, prior authorization for everolimus (Zortress) is not commonly utilized.

II. Everolimus (Afinitor Disperz) received FDA-approval for subependymal giant cell astrocytoma related to tuberous sclerosis complex (TSC), and TSC associated partial onset seizures for adult as well as pediatric patients. On the contrary, everolimus (Afinitor) has FDA-approval only for adult patients (18 years and older) for all approved indications.

III. Everolimus (Afinitor) has been evaluated in combination with exemestane for HR+, HER2-, advanced or metastatic breast cancer. In clinical trials, subjects had previously progressed on or after an aromatase inhibitor, such as, anastrozole or letrozole. Additionally, subjects may have received one or more previous lines of chemotherapy. The major efficacy outcome was progression-free survival (PFS) which was statistically significant versus placebo; however, an overall survival (OS) benefit was not shown.

IV. Everolimus (Afinitor) was evaluated for safety and efficacy in neuroendocrine tumors, including those of pancreatic, lung, and gastrointestinal origin. Subjects were allowed previous somatostatin analog use, and the major efficacy outcome, PFS, was statistically significant regardless of previous somatostatin use in comparison to placebo. Overall survival was not statistically different between the treatment arms.

V. Everolimus (Afinitor) has been evaluated for safety and efficacy in renal cell carcinoma in patients who have previously received sunitinib (Sutent), sorafenib (Nexavar), or both sequentially. Subjects may also have had bevacizumab (Avastin), interleukin 2, or interferon alpha. Progression-free survival was shown to be statistically significant in favor of everolimus (Afinitor); however, OS was not statistically different compared to placebo. Results may have been confounded by high rates of crossover from placebo to active therapy (80%).

VI. A phase two, randomized trial to study efficacy and safety of lenvatinib (Lenvima) in renal cell carcinoma included everolimus (Afinitor) as active comparator. Lenvatinib (Lenvima) was administered in combination with everolimus (Afinitor) to the participants in treatment arm. Subjects in treatment arm had progressed on previous anti-angiogenesis therapy (VEGF-targeted therapy) such as pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], or axitinib [Inlyta]. Primary outcome of progression-free survival (PFS) was shown to be statistically significant in favor of combination of lenvatinib (Lenvima) with everolimus (Afinitor) as compared to everolimus (Afinitor) monotherapy comparator. NCCN guidelines recommend everolimus (Afinitor) in combination with lenvatinib (Lenvima) and everolimus (Afinitor) monotherapy as category 1 and category 2A recommendations, respectively.

VII. Everolimus (Afinitor) was evaluated for safety and efficacy in tuberous sclerosis complex associated renal angiomyolipomas. Response rate was statistically significant in favor of everolimus (Afinitor), as well as the time to progression compared to placebo.

VIII. Everolimus (Afinitor, Afinitor Disperz) was evaluated in tuberous sclerosis completed-associated subependymal giant cell astrocytomas. Subjects included were of pediatric and adult populations. The primary outcome was SEGA response rate, which was statistically significant in favor of everolimus (Afinitor, Afinitor Disperz).

IX. Everolimus (Afinitor Disperz) was evaluated as an adjunct therapy for partial onset seizures associate with tuberous sclerosis complex (TSC). Subjects included were refractory to at least two conventional antiepileptic medications.

X. All strengths of Afinitor and Afinitor Disperz now have an AB-rated generic available. Medical necessity for brand Afinitor or Afinitor Disperz will be indicated by a contraindication to generic as intolerance to the generic is an indicator of intolerance to brand, given their therapeutic equivalence.

Investigational or Not Medically Necessary Uses

I. Carcinoid tumor
   A. Everolimus (Afinitor) was evaluated in a clinical trial for safety and efficacy for carcinoid tumor. The primary efficacy outcome was not reached, and overall survival outcomes favored placebo. At this time efficacy of everolimus (Afinitor) in this setting is not known to be clinically beneficial.

II. Everolimus (Afinitor, Afintor Disperz) has not been sufficiently evaluated for safety and/or efficacy, and/or is in clinical trials for the following indications:
   A. Graft-versus-host disease
   B. Ependymoma
   C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma
   D. Central nervous system cancers
   E. Kaposi's sarcoma
   F. Thymoma and thymic carcinoma
   G. Endometrial, ovarian, uterine cancers
   H. Prostate cancer
   I. Gastroesophageal carcinomas
   J. Waldenstrom macroglbulinemia

** 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. Afinitor, Afinitor Disperz [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. April 2018.
2. Baselga, K., Campone M., Piccart M., et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med.* 2012: 366(6): 520-529.
3. French JA., Lawson JA, Yapici Z., et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associagted with tuberous sclerosis: a Phase 3, randomized, double-blind, placebo-controlled study. *Lancet*. 2016: 388(10056):2153-2163.
4. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet*. 2008;372(9637):449-56.
5. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
6. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):514-23.
7. Franz DN, Belousova E, Sparagana S, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet*. 2013;381(9861):125-32.
8. Motzer RJ, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol. 2015 Nov;16(15):1473-1482.
9. U.S. Food&Drug Administration. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Accessed December 30, 2019.
10. NCCN guidelines for kidney cancer, version 01.2021; 07/15/2020. Accessed 10/08/2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to add in generic Afinitor Disperz and new generic Afinitor 10mg, updated all indications to allow brand coverage only if medical necessity established for brand over generic. Updated renewal section to carry over regimen requirements from initial (e.g., monotherapy use).	10/2021
Updated policy for renal cell carcinoma to allow after trial and failure of one prior anti-angiogenic therapy rather than only sorafenib (Nexavar) or sunitinib (Sutent); and combination of everolimus (Afinitor) with lenvatinib (Lenvima); Updated supporting evidence to include clinical data; Added supporting evidence for FDA-approvals based on age for everolimus (Afinitor) and everolimus (Afinitor Disperz)	10/2020
Generic everolimus 2.5 mg, 5 mg, and 7.5 mg added to the policy, with brand coverage only if medical necessity established for brand over generic.	01/2020
Prior authorization criteria transitioned to policy format, specialist providers updated to include neurologist, Addition of trial of conventional antiepileptic therapies prior to payment consideration for everolimus (Afinitor Disperz), addition of age requirement for everolimus (Afinitor), updated QLL for everolimus (Afinitor Disperz) to be calculated upon clinical review.	12/2019
Afinitor Disperz with indications added to criteria, formatting update and quantity limits changed to mirror available package sizes.	05/2018
Criteria created	05/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP326

Split Fill Management*

Description

This policy is intended to encompass medications that are considered experimental and investigational based on the quality of evidence provided in the clinical trials.

Length of Authorization

- Initial: N/A
- Renewal: N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
adagrasib (Krazati®)	• Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation	600 mg tablets	60 tablets/30 days
avapritinib (Ayvakit™)	• Unresectable or metastatic Gastrointestinal Stromal Tumor with a PDGFRA exon 18 mutation • Advanced Systemic Mastocytosis, including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm and mast cell leukemia	300 mg tablets	30 tablets/30 days
		200 mg tablets	
		100 mg tablets	
		50 mg tablets	
		25 mg tablets	
	• Indolent Systemic Mastocytosis	25 mg tablets	30 tablets/30 days
belzutifan (Welireg™)	• von Hippel-Lindau (VHL) disease associated with renal cell carcinoma (RCC), central nervous system (CNS), hemangioblastoma, or neuroendocrine tumors (pNET)	40 mg tablets	90 tablets/30 days
capmatinib (Tabrecta™)	• Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping	200 mg tablets	112 tablets/28 days
		150 mg tablets	
futibatinib (Lytgobi®)	• Intrahepatic cholangiocarcinoma, advanced or metastatic, with FGFR2 fusion or rearrangement	12 mg dose pack (84 tablets of 4 mg)	84 tablets/28 days
		16 mg dose pack (112 tablets of 4 mg)	112 tablets/28 days
		20 mg dose pack (140 tablets of 4 mg)	140 tablets/28 days
mobocertinib (Exkivity™)	• Metastatic non-small-cell lung cancer with exon 20 insertion mutation after progression on platinum-based chemotherapy	40 mg capsules	120 capsules/30 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

pemigatinib (Pemazyre™)	• Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma in adults with FGFR2 fusions or rearrangements	13.5 mg tablet	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
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
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
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	90 capsules/30 days
		80 mg capsules	60 capsules/30 days
		40 mg tablets	90 tablets/30 days
		80 mg tablets	60 tablets/30 days
		120 mg tablets	60 tablets/30 days
		160 mg tablets	60 tablets/30 days
sotorasib (Lumakras™)	• Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation	120 mg tablets	240 tablets/30 days
		320 mg tablets	60 tablets/30 days
tazemetostat (Tazverik™)	• 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	200 mg tablets	240 tablets/30 days
tepotinib (Tepmetko)	• Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping	225 mg tablets	60 tablets/30 days

Initial Evaluation

I. **All Medications listed in this policy** are considered investigational when used for all indications, including but not limited to, the following:

A. adagrasib (Krazati)
    1. Non-Small Cell Lung cancer (NSCLC)

B. avapritinib (Ayvakit)
    1. Gastrointestinal stromal tumor (GIST)
    2. Advanced systemic mastocytosis (AdvSM) [e.g., aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), mast cell leukemia (MCL)]
    3. Indolent systemic mastocytosis (ISM)

C. belzutifan (Welireg)
    1. VHL-disease associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastoma, or pancreatic neuroendocrine tumors (pNET)

D. capmatinib (Tabrecta)
    1. Non-Small Cell Lung Cancer

E. futibatinib (Lytgobi)
    1. Intrahepatic cholangiocarcinoma (iCCA)

F. mobocertinib (Exkivity)
    1. Non-Small Cell Lung Cancer

G. pemigatinib (Pemazyre)
    1. Cholangiocarcinoma
    2. Relapsed or refractory myeloid/lymphoid neoplasms (MLNs)

H. pirtobrutinib (Jaypirca)
    1. Relapsed or refractory mantle cell lymphoma (R/R MCL)
    2. Chronic lymphocytic leukemia (CLL)
    3. Small lymphocytic lymphoma (SLL).

I. pralsetinib (Gavreto)
    1. Non-Small Cell Lung Cancer (NSCLC)
    2. Thyroid Cancer

J. selpercatinib (Retevmo)
    1. Non-Small Cell Lung Cancer (NSCLC)
    2. Thyroid Cancer
    3. Other locally advanced or metastatic solid tumors with RET-fusion

K. sotorasib (Lumakras)
    1. Non-Small Cell Lung Cancer (NSCLC)

L. tazemetostat (Tazverik)
    1. Epithelioid sarcoma
    2. Non-Hodgkin lymphoma, including follicular lymphoma

M. tepotinib (Tepmetko)
    1. Non-Small Cell Lung Cancer (NSCLC)

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

A. adagrasib (Krazati)
    1. Has not been sufficiently studied for safety and efficacy for any condition to date
B. avapritinib (Ayvakit)
    1. Gastrointestinal Stromal Tumor (GIST)
    2. Advanced systemic mastocytosis (AdvSM, ASM, SM-ANH, MCL)
    3. Non-advanced, indolent systemic mastocytosis (ISM)
    4. Non-advance, smoldering systemic mastocytosis (SMM)
    5. Soft tissue sarcoma
    6. Solid tumors with or without CKIT or PDGFRA mutations
    7. Acute myeloid leukemia (AML) with or without CKIT or PDGFRA mutations
C. belzutifan (Welireg)
    1. Has not been sufficiently studied for safety and efficacy for any condition to date
D. capmatinib (Tabrecta)
    1. Has not been sufficiently studied for safety and efficacy for any condition to date
E. futibatinib (Lytgobi)
    1. Has not been sufficiently studied for safety and efficacy for any condition to date
F. mobocertinib (Exkivity)
    1. being withdrawn from the market based on the outcome of the Phase 3 EXCLAIM-2 confirmatory trial in the setting of metastatic non-small-cell lung cancer with exon 20 insertion mutation after progression on platinum-based chemotherapy 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. Takeda is working with the FDA towards the withdrawal of Exkivity from the U.S. market and will also withdrawal Exkivity globally where approved.
G. pemigatinib (Pemazyre)
    1. Has not been sufficiently studied for safety and efficacy for conditions other than cholangiocarcinoma and myeloid/lymphoid neoplasms to date.
       Cholangiocarcinoma
H. pirtobrutinib (Jaypirca)
    1. Pirtobrutinib (Jaypirca) used in combination with another oncology therapy
    2. 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.

3. 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.

4. Waldenström macroglobulinemia
5. Marginal zone lymphoma
6. Chronic graft versus host disease

I. pralsetinib (Gavreto)
   1. 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.
   2. Pralsetinib (Gavreto) has not yet been sufficiently studied for safety and efficacy for any condition.

J. selpercatinib (Retevmo)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

K. sotorasib (Lumakras)
   1. Has not been sufficiently studied for safety and efficacy for any condition to date

L. tazemetostat (Tazverik)
   1. Soft tissue sarcoma, including epithelioid sarcoma
   2. Non-Hodgkin lymphoma, including follicular lymphoma
   3. Other types of lymphoma, including but not limited to mediastinal, B-Cell, Mantle-Cell, Marginal Zone,
   4. Rhabdoid tumors
   5. Mesothelioma
   6. Kidney, bladder, urothelial cancers
   7. Hepatocellular carcinoma

M. tepotinib (Tepmetko)
    1. Has not been sufficiently studied for safety and efficacy for any condition to date

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

Supporting Evidence

adagrasib (Krazati)

I. Adagrasib (Krazati) is the second therapy FDA-approved for advanced or metastatic NSCLC that harbors a KRAS G12C mutation. It follows sotorasib (Lumakras), which received accelerated FDA approval in this setting, in 2021.
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, and 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. Adagrasib (Krazati) is a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy and is indicated for patients 18 years of age and older.
V. The New Drug Application (NDA) for adagrasib (Krazati) for the treatment of NSCLC was based on results from a subset of participants (cohort A) in an open-label, Phase 1/2, single-arm trial (KRYSTAL-1). Patients (N=116) with KRAS G12C mutated NSCLC, who had disease progression after platinum-based chemotherapy and/ or immunotherapy received adagrasib (Krazati) 600 mg orally twice daily for a median 15.7 months. The primary efficacy outcome was Objective Response Rate (ORR). Key secondary outcomes were Progression-free Survival (PFS), duration of response (DoR), and Overall Survival (OS). Adagrasib (Krazati) showed an ORR of 42.9% (95% CI; 33.5, 52.6), which included one patient (0.9%) complete response (CR) with remainder (n= 47) exhibiting partial responses. Additionally, participants in this cohort showed DoR of 8.5 months (95% CI; 6.2, 13.8), PFS 6.5 months (95% CI; 4.7, 8.4), and OS 12.6 months (95% CI; 9.2, 19.2).
VI. Based on the data from KRYSTAL-1 trial, the quality of the evidence to support efficacy of adagrasib (Krazati) 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.
VII. The safety of adagrasib (Krazati) was based on drug exposure during the clinical trial (N=116). All participants reported any grade adverse reactions (AE) with 81.9% suffering a grade ≥ 3 AE. The most common AE included diarrhea, nausea and vomiting, fatigue, dyspnea, and increased

creatinine and aspartate aminotransferase (AST). Anemia, hyponatremia, and dyspnea were reported as serious (grade ≥ 3) AE. Adagrasib (Krazati) led to 82.8% dose reduction or therapy interruptions, with 15.5% of patients requiring permanent discontinuation. Twenty (17.2%) patient deaths were reported during the trial, of which, two (1.7%) were ascribed as treatment-emergent (cardiac failure and pulmonary hemorrhage). Current patient exposure to adagrasib (Krazati) 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 adagrasib (Krazati) is largely unknown.

VIII. Currently, there are multiple clinical trials (Phase 1b / 2) ongoing for adagrasib (Krazati) in the settings of NSCLC, colorectal cancer, and other solid tumors harboring KRAS G12C mutation. Additionally, adagrasib (Krazati) 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 as of October 2022, data is not available for review.

IX. Single-arm, open-label clinical trial 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.

X. 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.

XI. 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) have 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). The efficacy and safety of targeted agents such as adagrasib (Krazati) in comparison with, or in combination with, currently established regimens, have not been studied and remain unknown.

XII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC 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, continued approval of adagrasib (Krazati) as a subsequent-line treatment of NSCLC, 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 adagrasib (Krazati), remains a practical option and an alternative path to treatment for qualifying patients.

avapritinib (Ayvakit)

I. Avapritinib (Ayvakit) is FDA-approved for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations, adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL), and adults with indolent systemic mastocytosis (ISM) whose symptoms are not adequately controlled by best supportive care (BSC).

II. Avapritinib (Ayvakit) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.

III. Avapritinib (Ayvakit) has not been sufficiently evaluated for safety and/or efficacy in combination with any other oncolytic medication. Avapritinib (Ayvakit) has been studied when used in combination with BSC therapies (e.g., antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc.) in patients with systemic mastocytosis.

IV. Due to the complex nature of treating any of the diagnoses listed above, treatment with avapritinib (Ayvakit) should be prescribed by, or in consultation with, an oncologist. When being requested for systemic mastocytosis, treatment may be prescribed by, an oncologist, allergist, immunologist gastroenterologist, or dermatologist.

V. **Gastrointestinal Stromal Tumors (GIST)**

   a. The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines state most PDGFRA mutations respond to imatinib (Gleevec), with the exception of PDGFRA D842V mutants, which do not respond to current TKI therapies [e.g. imatinib (Gleevec), sunitinib (Sutent), regorafenib (Stivarga)]. Avapritinib (Ayvakit) carries a category 2A recommendation as a preferred first line regimen for patients with unresectable, progressive, or metastatic GIST with a PDGFRA exon 18 mutations that are insensitive to imatinib (including PDGFRA D842V). Avapritinib (Ayvakit) is also listed under “useful in certain circumstances” as an additional treatment option after progression on approved therapies.

   b. GIST tumors have the following mutation prevalence: 75%-80% are KIT mutated, 5%-10% are PDGFRA mutated, and 10%-15% do not express KIT or PDGFRA. PDGFRA D842V mutants make up 60% of all PDGFRA mutations.

   c. In an international survey, imatinib (Gleevec) had a median progression free survival (PFS) of 2.8 months for patients with a D842V substitution and 28.5 months for patients with other PDGFRA mutations. In 46 months of follow-up, median overall survival was 14.7 months for patients with D842V substitutions and was not reached for patients with other PDGFRA mutations.

   d. Avapritinib (Ayvakit) was FDA-approved off interim analysis of one Phase 1, open-label, single-arm trial (NAVIGATOR) in 43 patients with unresectable or metastatic GIST that is PDGFRA positive. Patients included had previously tried and failed one or more previous TKIs. The primary efficacy outcome was overall response rate (ORR), and at interim analysis, it was 84% (95% CI 69, 93), and 89% (95% CI 75, 97) for the PDGFRA exon 18 group, and PDGFRA D842V group, respectively. Secondary outcomes included duration of response (DOR), and PFS, which were only reported for the PDGFRA D842V group. DOR was 27.6 months (95% CI 14.3, 27.6), and median PFS was 29.5 months (95% CI not reported).

1. At trial completion, the ORR in the *PDGFRA* D842V population (n = 56), 91% (51/56 patients). The DOR was 27.6 months (95% CI: 17.6 – not reached [NR]); the median PFS was 34.0 months (95% CI: 22.9 – NR); median OS was not reached.

e. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between drug use and 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.

f. The quality of the current evidence for avapritinib (Ayvakit) is considered low. The primary outcome, ORR, has not yet been correlated to clinically meaningful outcomes such as overall survival or quality of life parameters in GIST. The PFS result has unknown value due to the small sample size as well as the single arm, open-label design, and the medications significant safety profile. There is a lack of evidence indicated that avapritinib (Ayvakit) would provide a net health benefit for members.

g. Clinical trials initially started avapritinib (Ayvakit) at 400 mg daily but reduced the dose to 300 mg due to toxicity. Of the patients receiving 400 mg and 300 mg, 97% and 72% experienced AEs of grade ≥3 severity, respectively. There was no noted difference in efficacy between the 400 mg and 300 mg doses.

h. Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 22% permanent discontinuation rate due to intolerable adverse events.

i. Avapritinib (Ayvakit) has notable serious side effects for anemia (9%), abdominal pain (3%), pleural effusion (3%), sepsis (3%), gastrointestinal hemorrhage (2%), vomiting (2%), acute kidney injury (2%), pneumonia (1%), and tumor hemorrhage (1%). Almost all patients experienced one AE (99%), with the most common AEs (>20%) being: edema, nausea, fatigue, cognitive impairment, vomiting, decreased appetite, diarrhea, increased lacrimation, abdominal pain, constipation, rash, dizziness, and hair color changes. There are no specific contraindications to using avapritinib (Ayvakit); however, warnings and precautions include: intracranial hemorrhage, central nervous system effects (e.g., cognitive impairment, dizziness, sleep disorders), and embryo-fetal toxicity.

j. The VOYAGER trial was a randomized, open-label, phase 3 clinical trial evaluating PFS, ORR, and OS of avapritinib (Ayvakit) against regorafenib (Stivarga) in patients with locally advanced unresectable or metastatic GIST. There was no significant difference in median PFS between avapritinib and regorafenib in patients with molecularly unselected, late-line GIST. In May 2020, the FDA issued a complete response letter stating that it will not approve a new drug application for avapritinib for use in the treatment of adult patients with unresectable or metastatic fourth-line GIST based on data from VOYAGER.

VI. **Advanced Systemic Mastocytosis (AdvSM)**

a. Systemic mastocytosis (SM) is a rare, clonal neoplastic proliferation of mast cells driven by the *KIT*D816V mutation, resulting in uncontrolled proliferation and activation of abnormal mast cells in various tissues, including skin, bone marrow, gastrointestinal

tract, liver, spleen, and lymph nodes. Advanced systemic mastocytosis (AdvSM) accounts for approximately 5% of all SM cases and includes the following disease variants: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).

b. According to NCCN guidelines for systemic mastocytosis, as of May 2022, treatment options for AdvSM include cytoreductive therapy, allogenic HCT, and enrollment in clinical trials. Cytoreductive therapies include avapritinib, midostaurin, cladribine, imatinib, and peginterferon alfa-2a ± prednisone. The guidelines note the following treatment considerations for AdvSM, all with category 2A recommendations:
    1. Preferred regimens: Avapritinib and midostaurin
    2. Other recommended regimens: Cladribine for patients that may require when rapid debulking of disease. Peginterferon alfa-2a, has a cytostatic mechanism of action and may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction
    3. Useful in certain circumstance: Imatinib is FDA-approved for adult patients with ASM without the KIT D816V mutation (including wild-type) or with unknown mutational status. Imatinib included as a treatment option for patients with ASM (for KIT D816V mutation negative or unknown, WDSM, or if eosinophilia is present with FIP1L1-PDGFRA fusion gene may also be considered as another treatment option for patients diagnosed with ASM or SM-ANH.

c. Avapritinib (Ayvakit) was FDA-approved based on the data from one phase 1 (EXPLORER) and a prespecified interim analysis of the phase 2 (PATHFINDER) multicenter, single-arm, open-label clinical trials. Patients were considered evaluable if they had a confirmed diagnosis of AdvSM per World Health Organization (WHO) and met modified international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline. There were 48 evaluable patients in the EXPLORER trial and 32 patients in the PATHFINDER trial at interim analysis. The primary efficacy endpoint in the PATHFINDER trial was overall response rate (ORR), which was 75%. A favorable ORR was observed in the EXPLORER trial, which was 75% (95% CI, 62 – 86). Additional efficacy outcome measures included duration of response (DOR) and time to response; the median DOR for all evaluable patients was 38.3 months (95% CI, 19, not estimable) and time to response was 2.1 months.

d. A pooled efficacy and safety analysis from the EXPLORER and PATHFINDER trials compared avapritinib and best available therapy in patients with AdvSM who received ≥1 systemic therapy prior to avapritinib. The ORR in n=31 evaluable patients was 71% (95% CI: 52 – 86), including 19% with complete remission (CR)/CR with partial recovery of peripheral blood counts (CRh). Median OS was not reached (median follow-up 17.7 months). Median time to response was 2.3 months, median time to CR/CRh was 7.4 months. The median duration of response (DOR) was not reached. Median OS was significantly improved in patients treated with avapritinib (49.0 months [95% CI, 46.9 months–not estimable] vs. 26.8 months [95% CI, 18.2–39.7 months]; adjusted HR, 0.48;

95% CI, 0.29–0.79; P = .004). Data further demonstrated that avapritinib treatment was associated with improved OS compared to midostaurin (HR, 0.59; 95% CI, 0.36–0.97; P < .001) and cladribine (HR, 0.32; 95% CI, 0.15–0.67; P = .003). OS was also improved in patients with SM-AHN treated with avapritinib compared to best available therapy. The efficacy of avapritinib in patients with AdvSM was established irrespective of prior therapies or S/A/R mutation status.

e. 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.
f. Based on information from the EXPLORER and PATHFINDER trials, the quality of evidence is considered low at this time given the single-arm, open-label trial design and use of surrogate marker as the primary efficacy outcome. At this time, there is no correlation between ORR and clinically meaningful outcomes of morbidity and mortality or quality of life parameters. Therefore, the true efficacy of the medication remains unknown. The medication also has a significant safety profile that is under post-marketing review by the FDA. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members.
g. Avapritinib (Ayvakit) is associated with notable serious side effects, including anemia (5%), subdural hematoma (4%), pleural effusion, ascites and pneumonia (3% each), acute kidney injury, gastrointestinal hemorrhage, intracranial hemorrhage, encephalopathy, gastric hemorrhage, large intestine perforation, pyrexia, and vomiting (2% each). Grade ≥3 cytopenias occurred in up to one-quarter of patients and facial/periorbital edema (any grade) in one-half (3 percent grade ≥3 facial/periorbital edema). No new safety signals were observed during the clinical trials for AdvSM.
h. In patients with AdvSM, a platelet count must be performed prior to initiating therapy and every 2 weeks first the first 8 weeks of starting therapy. Thrombocytopenia is listed as a warning/precaution for therapy when used in patients with AdvSM. Avapritinib (Ayvakit) is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L.
i. The FDA has issued a post-marketing requirement to provide additional evaluation of the safety signals of intracranial hemorrhage and cognitive adverse reactions associated with avapritinib (Ayvakit), which can only be adequately assessed in clinical trials. This trial is anticipated to be submitted by 12/2021. The FDA has also issued a second post-marketing requirement to submit the completed phase 2 PATHFINDER trial data, which is anticipated to be completed 1/2026.

VII. **Non-advanced, indolent systemic mastocytosis (ISM)**

a. Indolent systemic mastocytosis (ISM) is defined as a rare, usually benign, chronic, form of systemic mastocytosis characterized by an abnormal accumulation of neoplastic mast cells mainly in the bone marrow, but also in other organs or tissues such as the skin. ISM accounts for more than 70% of all SM cases in published literature. One of the key

diagnostic determinants that differentiates ISM from other SM subtypes includes absence of C-findings (are indicative of organ damage produced by mast cell infiltration via biopdy), no evidence of an associated hematologic neoplasm, low mast cell burden, and higher prevalence of skin lesions. Patients with ISM have a near-normal life expectancy, and ISM carries a low risk of progression with < 3% of patients progressing to a more severe form of systemic mastocytosis. The most common cause of death is disability or anaphylaxis.

b. Avapritinib (Ayvakit) is the first FDA-approved therapy for ISM. Approval was based on data from the randomized, double-blind, placebo-controlled part of the PIONEER trial, 141 patients received avapritinib (Ayvakit) 25 mg once daily + best supportive care (BSC) and 71 patients received placebo + BSC. The study included adults with an indolent SM diagnosis confirmed by central pathology review, and moderate-to-severe symptom burden despite an optimized regimen of BSC, which may include antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc. All patients were able to continue symptom-directed therapy throughout the trial and, following completion of the 24-week treatment period, had the option to receive avapritinib (Ayvakit) in an open-label extension study (HARBOR trial). The primary endpoint was the change in patient-reported disease symptoms as assessed by the ISM Symptom Assessment Form (ISM-SAF) total symptom score (TSS) Key secondary endpoints include mean change in individual symptom scores of ISM-SAF, change in most severe symptom score, QoL, and several biomarkers of mast cell burden. Avapritinib (Ayvakit) achieved a statistically significant improvement in TSS compared to placebo at 24 weeks (p=0.003) and demonstrated statistically significant differences all key secondary endpoints, observed with improvements in severe symptoms and across all symptoms measured by the ISM-SAF that deepened over time.

c. The most common treatment-related AEs were headache (8 %), nausea (6%), peripheral edema (6%), periorbital edema (6%), and dizziness (3%). Across treatment arms, most adverse events were mild to moderate in severity, and treatment-related AEs leading to discontinuations were low for both arms (< 2% each). No new safety signals were observed during the clinical trials for ISM.

d. Data from this trial are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. It is unclear whether avapritinib (Ayvakit) provides a clinically meaningful improvement in a condition that is already indolent. Furthermore, the NCCN guideline acknowledges that the IWG-MRT-ECNM response criteria were developed mainly for use in clinical trials and may not be widely used in clinical practice. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members with an already indolent form of SM.

e. The NCCN guidelines recommend observation or treating mast cell activation symptoms with best supportive care in patients with symptomatic ISM. The guidelines do not have any pharmacotherapies listed in their treatment algorithm for ISM nor have avapritinib (Ayvakit) noted as a potential therapy option for ISM. Furthermore, the NCCN guidelines encourages enrollment in well-designed clinical trials investigating novel therapeutic strategies regardless of SM type. As of May 2023, an expanded access program (EAP)

(NCT04714086) for avapritinib for patients with ISM is available, which may provide access to therapy in lieu of clinical trial enrollment.

belzutifan (Welireg)

I. Belzutifan (Welireg) is the first systemic therapy FDA-approved for the treatment of adult patients with von Hippel-Lindau (VHL) disease associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastoma, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. It is also the only orally administered drug indicated in this setting.

II. Von Hippel-Lindau syndrome (VHL) is a hereditary condition associated with tumors arising in multiple organs. VHL-related tumors include hemangioblastomas, which are blood vessel tumors of the brain, spinal cord, and retina. Patients with VHL also have an increased risk of developing clear cell renal cell carcinoma (cc-RCC), pheochromocytoma, or pancreatic neuroendocrine tumor (pNET). Initial features of VHL include kidney cysts, pancreatic cysts, epididymal cystadenomas, broad ligament cystadenomas, and endolymphatic sac tumors (ELST), which are tumors of the inner ear that may cause hearing loss.

III. Patients with VHL disease may present with cysts in any one or multiple organ systems. For example, it is possible for a patient to show radiographic presence of pNET or other neuroendocrine lesions without presence of kidney lesions. However, the prevalence data shows kidney lesions and cc-RCC as the most common progressive manifestation in VHL (up to 70% of cases). On the other hand, pNET, hemangioblastoma, pheochromocytoma may be prevalent between 5% and 30% of the VHL cases.

IV. Additionally, VHL disease associated tumors are slow growing in nature. Depending on the tumor type, natural evolution and progression for VHL tumors may be between four years to 10 years after onset. Onset of symptoms is mostly observed in adulthood with median age of onset 24 to 44 years of age.

V. VHL protein deactivation followed by HIF-2α buildup may be one of the key drivers to VHL-associated tumorigenesis. Unregulated levels of HIF-2α may stimulate several oncogenes associated with angiogenesis and tumor growth, leading to both benign and malignant tumors.

VI. The only way to diagnose VHL is with genetic testing. Nearly all patients with VHL will be found to have a genetic mutation in their *VHL* gene once tested. There are no universal guidelines regarding who should be screened for VHL. However, VHL should be suspected when a person has a family history of VHL.

VII. There are no FDA-approved systemic therapies for VHL associated tumors. Current standard of care (irrespective of tumor type at diagnosis) involves active surveillance, surgical resection when necessary (e.g., partial nephrectomy or ablation) and radiation (e.g., for spinal cord tumors). Active surveillance may involve radiographic imaging, biomarker screenings, and histological study. When tumors/cysts reach resectable mass (e.g., for RCC a 3 cm rule is followed), the patient may undergo resection. A patient may have to undergo multiple resections over lifetime. It is important to note that for initial manifestations, as well as lesions presenting later during life, surgical resection remains standard of care as long as the tumor/ lesions are determined to be benign.

VIII. For patients who progress to advanced carcinomas with metastatic potential, guideline recommended systemic therapies (e.g., tyrosine kinase inhibitors (TKI), vascular endothelial growth factor (VEGF) inhibitors) may be warranted as indicated for the tumor type and location. The National Comprehensive Cancer Network (NCCN) treatment guideline for kidney cancer (RCC) has included belzutifan (Welireg) as a Category 2A recommendation for systemic therapy

for confirmed hereditary RCC associated with VHL disease. There are no treatment guidelines specific to the pharmacological management of the VHL disease.

IX. **Clinical Trial Data**:

- Belzutifan (Welireg) received FDA-approval based on an ongoing Phase 2, open-label, single-arm trial (Study004). Patients (N= 61) with VHL- associated cc-RCC (≥ 1 measurable localized tumor in the kidney and pancreas), received belzutifan (Welireg) 120 mg orally once a day for a median of 21.8 months. Primary efficacy outcome was Overall Response Rate (ORR) in RCC. Key secondary outcomes were ORR in non-RCC lesions, Progression-Free Survival (PFS), and Duration of Response (DoR). All participants were not candidates for immediate surgery and were naïve to chemotherapy. The study excluded patients with metastatic disease. Therapy with belzutifan (Welireg) for a median of 21.8 months showed 49.2% ORR (95% CI; 36.1, 62.3), all of which were partial responses (PR). DoR and PFS were not estimable currently. Additionally, patients with pancreatic lesions (n=61), pancreatic neuroendocrine tumors (pNET; n= 12), and CNS hemangioblastoma (n= 24) exhibited 77%, 83%, and 62% ORR, respectively.
- Belzutifan (Welireg) showed significant safety concerns with common adverse reactions (AE): anemia (90.2%), fatigue (65%), headache (41%), nausea (34%), and dyspnea (23%). Serious AE (grade 3, 14.8% patients) included anemia, fatigue, dyspnea and hypertension, pneumonitis, and elevation of liver enzymes. Although no contraindications are listed, the drug information includes warnings of serious anemia and hypoxia. Treatment during clinical trial led to 39% therapy interruptions, 13% dose reductions, 3.3% discontinuations, and one death. The real-world safety profile of belzutifan (Welireg) remains undetermined at this time.
- Additionally, a Phase 1, open-label, single arm clinical trial for belzutifan (Welireg) studied safety and efficacy of belzutifan (Welireg) in advanced cc-RCC. Enrolled patients in this trial had advanced cc-RCC with ECOG PS 1 through ≥ 3. All patients were treatment experienced (62% had ≥3 systemic therapies) with majority (91%) exposed to vascular endothelial growth factor (VEGF) inhibitors, along with mTOR inhibitors and checkpoint inhibitors. At median 27.7 months of follow-up, belzutifan (Welireg) treatment led to a 25% ORR (95%CI; 15, 39) in the cc-RCC cohort.

X. FDA-approval for belzutifan (Welireg) followed an accelerated approval pathway. Continued approval may be contingent upon verification of clinical benefits in confirmatory trials. Currently, clinical trials are underway for advanced cc-RCC as monotherapy as well as in combination with other oncolytic agents.

XI. Therapies based on targeting molecular pathways in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the pharmacological management of cancers. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Specifically, in the setting of VHL-associated tumors, this resistance may be associated with feedback activation of other downstream pathways such as vascular endothelial growth factor (VEGF), platelet derived growth factor receptor beta (PDGFRβ), and hypoxia inducible factor-1 (HIF-1) mediated oncogenesis. Thus, selective inhibition of HIF-2α (which is found mainly in renal cells) by belzutifan (Welireg) may not provide a clear path to complete suppression of VHL-associated tumors.

XII. Proposed place in therapy for belzutifan (Welireg) is as an initial (first-line) agent for the treatment of VHL associated tumors in patients, who do not require immediate surgery; and it may be considered an option to prolong progression to malignancy and/or surgery. However, available clinical data do not support clinically meaningful outcomes in mortality, quality of life,

and morbidity (e.g., measurable reduction in the need for surgery, and/ or progression to malignancy). At this time, the quality of the available evidence is considered low. Although an acceptable surrogate marker in oncology, ORR does not establish true causal relation between the intervention and effect. Given the slow natural progression of VHL disease, lack of comparator, and open-label trial design, medication efficacy and true clinical value of belzutifan (Welireg) remains uncertain.

capmatinib (Tabrecta)

I. Capmatinib (Tabrecta) is the first therapy FDA-approved for NSCLC with a mutation that leads to MET 14 exon 14 skipping. Other therapies that may be used in this setting include tepotinib (Tepmetko), crizotinib (Xalkori®), platinum-based doublet chemotherapy with or without bevacizumab, and/or immunotherapy (e.g., nivolumab, pembrolizumab); however, available data is limited and response in this population is generally poor.

II. Capmatinib (Tabrecta) is FDA-approved in the metastatic setting. It was evaluated in GEOMETRY mono-1, an open-label, Phase 2, multi-cohort, single-arm trial. Patients with METex14 skipping mutation or MET-amplified disease across various treatment settings (e.g., treatment naïve vs pretreated) were included. Initial FDA-approval under accelerated pathway, was based on those with METex14 skipping mutation only, Cohorts 4 and 5b. Cohort 4 patients were previously treated with one or two lines of therapy and Cohort 5b included treatment-naïve patients. Patients had MET-dysregulated advanced NSCLC, with absence of EGFR or ALK mutations. Full FDA approval was granted based on additional data from Cohorts 6 and 7. Cohort 6 patients were previously treated, with majority receiving one prior line of therapy and Cohort 7 patients were treatment naïve. Cohorts 6 and 7 included patients with METex14 skipping mutation.

III. Primary efficacy outcomes were Overall Response Rate (ORR) and Duration of Response (DoR). Secondary outcomes were Progression-free Survival (PFS) and Overall Survival (OS); however, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life. Capmatinib (Tabrecta) was FDA-approved under the accelerated approval pathway based on ORR and DoR. Conversion to regular FDA approval was based on additional ORR and DoR data for 63 patients as well as an additional 22 months of follow up. Despite receiving regular FDA approval, the medication efficacy continues to remain uncertain. There a several trials underway for NSCLC and other cancer types.

IV. The safety of capmatinib (Tabrecta) is based on patients from all cohorts (n=334). There were 37% of patients that were exposed to therapy for at least six months and 22% were exposed for at least one year. The most common adverse events include peripheral edema, nausea, fatigue, vomiting, dyspnea, and anorexia.

V. Serious adverse events occurred in 53% of patients and included dyspnea, pneumonia, pleural effusion, physical health deterioration, and peripheral edema. These events occurred in at least 2% of patients, and there was one case of fatal pneumonitis. There are no contraindications. Capmatinib (Tabrecta) showed a 54% dose interruption rate, a 23% dose reduction rate, and a 16% permanent discontinuation rate due to adverse events.

VI. As of January 2023, The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC with a mutation that leads to MET exon 14 skipping give capmatinib (Tabrecta) a Category 2A, preferred recommendation. Tepotinib (Tepmetko) is also a preferred, Category 2A

recommended treatment option. Crizotinib (Xalkori) has a Category 2A recommendation, useful in certain circumstances. These circumstances are not defined in the guideline.

VII. 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.

futibatinib (Lytgobi)

I. Futibatinib (Lytgobi) is a selective inhibitor of fibroblast growth factor receptor 1-4 (FGFR), FDA-approved for adult patients with previously treated, unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma (iCCA) harboring an FGFR2 fusion or other rearrangements. Futibatinib (Lytgobi) is a once-daily orally administered tablet.

II. Futibaitinib (Lytgobi) is the third FGFR2 inhibitor and joins infigratinib (Truseltiq) and pemigatinib (Pemazyre), which are indicated for previously treated patients with advanced or metastatic CCA. It should be noted that as of March 2023, infigratinib (Truseltiq) is scheduled to be withdrawn from the US market.

III. The FDA approval for futibatinib (Lytgobi) is limited only to the treatment of iCCA. On the other hand, pemigatinib (Pemazyre) carris a broader FDA-approved indication for the treatment of CCA (iCCA and eCCA). National Comprehensive Cancer Network (NCCN) guidelines have included Futibaitinib (Lytgobi) alongside pemigatinib (Pemazyre) and infigratinib (Truseltiq) as a subsequent-line therapy, useful in CCA with FGFR2 mutations (Category 2A).

IV. Futibaitinib (Lytgobi) was studied in an ongoing open-label, single-arm, multi-cohort phase 1/ 2 trial (N= 103). Patients with unresectable, advanced, or metastatic iCCA, who had received at least one prior platinum-based systemic therapy were administered futibatinib (Lytgobi) for a median of 9.1 months. At median follow-up, an objective response rate (ORR) of 41.7% (95% CI, 32, 52) was reported, with all participants reporting a partial response (PR). Additionally, a median PFS of 8.9 months and median OS of 20 months were observed.

V. Futibaitinib (Lytgobi) was FDA-approved under the accelerated approval pathway. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

VI. The quality of evidence is considered low due to single-arm, open-label study design with unknown impact on clinically meaningful outcomes such as morbidity, mortality, health-related quality-of-life, or symptom improvement in treated patients. OS remains an exploratory outcome due to the observational study design and requires confirmation in a subsequent clinical trial. Additionally, the efficacy of futibatinib (Lytgobi) in comparison with, as well as after progression on pemigatinib (Pemazyre) remains unknown.

VII. Most CCA patients present with advanced-stage or unresectable tumors at diagnosis, wherein platinum-based chemotherapy (cisplatin with gemcitabine and/ or durvalumab (Imfinzi)) remains the standard of care. For patients, who progress on the first-line therapy, FOLFOX is the preferred subsequent-line option, along with 5-fluorouracil (5-FU), capecitabine, and paclitaxel as alternatives. Targeted therapies may be considered as subsequent-line options based on the presence of amenable mutations (e.g., entrectinib (Rozlytrek) and larotrectinib (Vitrakvi) for CCA with NTRK gene fusions).

VIII. Currently, there are other clinical trials (Phase 1b / 2) ongoing for futibatinib (Lytgobi) in the settings of metastatic breast cancer, cholangiocarcinoma, endometrial cancer, urothelial cancer etc. as a monotherapy as well as in combination with other agents (e.g., binimitinib, pembrolizumab). These clinical trials are in early phases and as of January 2023, data is not available for review.

IX. Single-arm, open-label clinical trial 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, Overall Response Rate (ORR), despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. ORR is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

X. Targeted therapies in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the management of CCA 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 presents a major clinical challenge. Additionally, the targeted therapy approach is also susceptible to failure due to escape mutations. To date, the clinical data for FGFR2 inhibitors do not support robust conclusions regarding their safety, efficacy, and long-term impact on disease outcomes.

XI. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines note that the best management for any patient with cancer is in a clinical trial setting, and participation in a trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading healthcare 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 iCCA. Despite the accelerated FDA approval, continued approval of futibatinib (Lytgobi) as a subsequent-line treatment of iCCA, remains contingent upon verification of clinical benefit in confirmatory trials.

mobocertinib (Exkivity)

I. Mobocertinib (Exkivity) is an oral EGFR tyrosine kinase inhibitor (TKI) that is being evaluated for exon 20 insertion mutant-positive NSCLC (EGFRex20ins-NSCLC) in those that have had disease progression on platinum-based chemotherapy. This specific type of NSCLC is thought to account for 2-3% of NSCLC cases annually, and is more commonly seen in those that do not have a smoking history.

II. Mobocertinib (Exkivity) is the second therapy specifically FDA-approved for EGFRex20ins-NSCLC. Amivantamab-vmjw (Rybrevant), an IV human antibody, was FDA-approved in May 2021. Approval was based off of the Phase 1 CHYRSALIS trial, a single-arm, open-label trial in 81 patients that previously progressed on platinum chemotherapy.

III. Platinum-based chemotherapy is utilized first-line for this condition, and is considered standard of care. Mobocertinib (Exkivity) is the first TKI specifically FDA-approved for this mutation. Other EGFR TKIs (e.g., osimertinib [Tagrisso]) have been used in this setting off-label; however, most cases of EGFRex20ins-NSCLC are resistant to those therapies.

IV. Interim results of the Phase 1/2 trial are being used to support accelerated FDA-approval. Mobocertinib (Exkivity) was granted Priority Review, as well as Breakthrough Therapy, Fast Track and Orphan Drug designations. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. Continued Phase 2, as well as Phase 3 trials are underway to assess safety and efficacy. Both of these therapies are expected to be

utilized in the second-line treatment setting; however, given expected preference for the targeted indication – use in the first-line setting may appeal to patients and providers. Mobocertinib (Exkivity) is being evaluated in a Phase 3, open-label trial versus platinum-based chemotherapy in patients with advanced or metastatic EGFRex20ins-NSCLC. Per ClinicalTrials.gov, the study is recruiting; however, there have been potential pauses in recruitment due to futility analyses.

V. Mobocertinib (Exkivity) is being evaluated in a Phase 1/2, single-arm, open-label trial in 114 patients with metastatic EGFRex20ins-NSCLC that were previously treated with platinum chemotherapy. Interim results showed an overall response rate (ORR). Other trial outcomes include duration of response (DoR), and progression-free survival (PFS). The quality of the evidence is low given the open-label and single-arm trial design, and small sample size. True medication efficacy is unknown due to the observational nature of the data. Additionally, the endpoints evaluated have not been correlated with meaningful outcomes such as improved survival or quality of life. The results are similar to those seen for amivantamab-vmjw (Rybrevant). Use of this therapy in any treatment setting is considered experimental and investigational at this time given the unknown clinical benefit and ongoing clinical trials to evaluate safety and efficacy.

VI. The safety profile is based on the 114 patients that have received therapy to date. Treatment related adverse events (AE) occurred in 99% of patients. Common AE: diarrhea 91%, rash (45%), paronychia (38%), decreased appetite (35%), nausea (34%), dry skin (31%), vomiting (30%), increased creatinine (25%), stomatitis (24%), pruritus (21%). Grade 3-4 AE occurred in 47% and 49% of patients were documented to have serious AE. Dose reduction due to AE occurred in 25% of patients, and AE leading to treatment discontinued occurred in 17% of patients. One patient experienced cardiac failure, a TRAE leading to death. Given the observational nature of the data in a small population, the severity and extent of AE that are due to the drug versus the disease are unknown at this time.

VII. NCCN guidelines for advanced or metastatic EGFRex20ins-NSCLC recommend platinum-based combination chemotherapy for first-line treatment, this is a Category 1 recommendation. Mobocertinib (Exkivity) and amivantamab-vmjw (Rybrevant) have been added as subsequent therapy options (Category 2A recommendation). The recommendations are specific to patients with an ECOG score 0-2, and for those with PS 3-4, best supportive care is recommended (Category 2A recommendation). Clinical trials are highly encouraged for all settings. ASCO provides similar recommendations for platinum-based combination chemotherapy in the first-line setting; however, have not been updated to include the targeted therapies. Guidelines do not recommend conventional EGFR TKIs for this mutation, and ASCO recommends platinum chemotherapy after progression on a conventional EGFR TKI if one was utilized.

VIII. 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.

emigatinib (Pemazyre)
<u>Treatment of Cholangiocarcinoma</u>

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).

pirtobrutinib (Jaypirca)

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.

pralsetinib (Gavreto)

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.

selpercatinib (Retevmo)

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.

sotorasib (Lumakras)

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.

tazemetostat (Tazverik)

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.

tepotinib (Tepmetko)

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.

** 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

adagrasib (Krazati®)

1. Jänne PA, Riely GJ, et al. Adagrasib in Non-Small-Cell Lung Cancer Harboring a *KRASG12C* Mutation. N Engl J Med. 2022 Jul 14;387(2):120-131.
2. Takamasa K, Suda K, et al. KRAS Secondary Mutations That Confer Acquired Resistance to KRAS G12C Inhibitors, Sotorasib and Adagrasib, and Overcoming Strategies: Insights From In Vitro Experiments. J Thor Oncol. 2021 16 (8): 1321-1332.
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 V3.2022. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated March 16, 2022.

avapritinib (Ayvakit™)

1. Ayvakit [Prescribing Information]. Blueprint Medicines: Cambridge, MA. March 2023.

2. Ayvakit [Manufacturer e-dossier]. Blueprint Medicines: Cambridge, MA. June 2021.
3. National Comprehensive Cancer Network. NCCN Guidelines: Gastrointestinal Stromal Tumors. Version 1.2023. Accessed April 28, 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf.
4. Casali PG, Abecassis N, Aro HT, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv68-iv78.
5. Heinrich M, Jones RL, von Mehren M, et al. Clinical Response to Avapritinib by RECIST and Choi Criteria in ≥4th Line and PDGFRA Exon 18 Gastrointestinal Stromal Tumors (GIST). Presented at: Connective Tissue Oncology Society 2019 Annual Meeting. November 15, 2019; Tokyo, Japan.
6. Jones RL, et al. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumors: Long-term efficacy and safety data from the NAVIGATOR phase 1 trial. European Journal of Cancer. 145(2021); 132-142.
7. Kang Y-K, George S, Jones RL, et al. Avapritinib versus regorafenib in locally advanced unresectable or metastatic GI stromal tumor: a randomized, open-label phase III study. J Clin Oncol. Published online August 3, 2021. doi:10.1200/JCO.21.00217
8. Blueprint Medicines receives complete response letter from FDA for avapritinib new drug application for the treatment of fourth-line gastrointestinal stromal tumor. News release. Blueprint Medicines. May 15, 2020. Accessed April 28, 2023. https://ir.blueprintmedicines.com/news-releases/news-release-details/blueprint-medicines-receives-complete-response-letter-fda
9. National Comprehensive Cancer Network. NCCN Guidelines: Systemic Mastocytosis. Version 2.2022. Accessed April 28, 2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf.
10. Gotlib J. Advanced systemic mastocytosis: Management and prognosis. In: Post T, ed. UpToDate. UpToDate; 2022. Accessed April 24, 2023. www.uptodate.com
11. DeAngelo DJ, et al. PATHFINDER: Interim Analysis of Avapritinib in Patients with Advanced Systemic Mastocytosis (AdvSM). Presented at the American Association for Cancer Research Annual Meeting. May 2021.
12. Radia DH, et al. Avapritinib induces responses in patients with advanced systemic mastocytosis (AdvSM), regardless of prior midostaurin therapy. Poster Presentation at BSH 2021 Virtual ASM. April 2021.
13. Evans EK, Gardino AK, Kim JL, et al. A precision therapy against cancers driven by *KIT/PDGFRA* mutations. *Sci Transl Med*. 2017;9(414):eaao1690. doi:10.1126/scitranslmed.aao1690
14. Reiter A, Gotlib J, Álvarez-Twose I, et al. Efficacy of avapritinib versus best available therapy in the treatment of advanced systemic mastocytosis. *Leukemia*. 2022;36(8):2108-2120. doi:10.1038/s41375-022-01615-z
15. Reiter A, Gotlib J, Álvarez-Twose I, et al. P1014: OVERALL SURVIVAL IN PATIENTS WITH ADVANCED SYSTEMIC MASTOCYTOSIS RECEIVING AVAPRITINIB VERSUS MIDOSTAURIN OR CLADRIBINE. *Hemasphere*. 2022;6(Suppl):904-905. Published 2022 Jun 23. doi:10.1097/01.HS9.0000846924.89785.04
16. Reiter A, Schwaab J, DeAngelo DJ, et al. Efficacy and safety of avapritinib in previously treated patients with advanced systemic mastocytosis. *Blood Adv*. 2022;6(21):5750-5762. doi:10.1182/bloodadvances.2022007539
17. DeAngelo DJ, Radia DH, George TI, et al. An updated analysis on safety and efficacy of avapritinib in patients with advanced systemic mastocytosis from the explorer clinical study: long-term efficacy and safety. *Blood*. 2022;140(Supplement 1):3932-3934.
18. Gotlib J, Schwaab J, Shomali W, et al. Proposed European Competence Network on Mastocytosis-American Initiative in Mast Cell Diseases (ECNM-AIM) Response Criteria in Advanced Systemic Mastocytosis. *J Allergy Clin Immunol Pract*. 2022;10(8):2025-2038.e1. doi:10.1016/j.jaip.2022.05.034
19. Hartmann K, Escribano L, Grattan C, et al. Cutaneous manifestations in patients with mastocytosis: consensus report of the european competence network on mastocytosis; the american academy of allergy, asthma & immunology; and the european academy of allergology and clinical immunology. Journal of Allergy and Clinical Immunology. 2016;137(1):35-45.
20. Weiler CR, Austen KF, Akin C, et al. Aaaai mast cell disorders committee work group report: mast cell activation syndrome (Mcas) diagnosis and management. Journal of Allergy and Clinical Immunology. 2019;144(4):883-896.
21. Pardanani A. Systemic mastocytosis in adults: 2021 Update on diagnosis, risk stratification and management. Am J Hematol. 2021;96(4):508-525. doi:10.1002/ajh.26118
22. Akin C. Indolent and smoldering systemic mastocytosis: Management and prognosis. In: Post T, ed. UpToDate. UpToDate; 2021. Accessed May 1, 2023. www.uptodate.com
23. Study to Evaluate Efficacy and Safety of Avapritinib (BLU-285), A Selective KIT Mutation-targeted Tyrosine Kinase Inhibitor, Versus Placebo in Patients With Indolent Systemic Mastocytosis (PIONEER). ClinicalTrials.gov identifier: NCT03731260. Updated September 20, 2022. Accessed May 1, 2023.

24. Study to Evaluate Efficacy and Safety of BLU-263 Versus Placebo in Patients With Indolent Systemic Mastocytosis (HARBOR). ClinicalTrials.gov identifier: NCT04910685. Updated April 6, 2023. Accessed May 1, 2023.
25. Akin C, Norregaard C, Roche M, Sullivan E, Siebenhaar F. Utility of a validated disease-specific measure to assess symptomology in patients with indolent systemic mastocytosis (ISM). Poster #220. Presented at the 2023 AAAAI Annual Meeting, February 24-27, 2023.
26. Castells M, Gotlib J, Henneke OE, et al. Detailed data from registrational PIONEER study demonstrate broad impact of AYVAKIT in patients with ISM. Powerpoint Presentation. Presented at the 2023 AAAAI Annual Meeting, February 27, 2023. https://ir.blueprintmedicines.com/static-files/60f73c28-4394-48e5-952a-e75a8d558250
27. Expanded Access Program (EAP) for Avapritinib. ClinicalTrials.gov identifier: NCT04714086. Updated November 17, 2022. Accessed May 1, 2023.

belzutifan (Welireg™)

7. Belzutifan (Welireg) [Prescribing Information]. Merck Sharp & Dohme Corp., Whitehouse Station, NJ. August 2021.
8. Srinivasan R, Donskov F, Iliopoulos O, et al. Phase 2 Study of Belzutifan (MK-6482), an Oral Hypoxia inducible Factor 2α Inhibitor, for Von Hippel-Lindau Disease–associated Clear Cell Renal Cell Carcinoma. Abstract #4555. Presented at: American Society of Clinical Oncology (ASCO); June 4-8, 2021; Virtual Meeting.
9. Jonasch E, Donskov F, Iliopoulos O, et al. Phase 2 study of the oral HIF-2α inhibitor MK-6482 for Von Hippel-Lindau disease-associated renal cell carcinoma. Abstract #5003. Presented at: American Society of Clinical Oncology (ASCO); May 29-31, 2020; Virtual Meeting.
10. NCCN Clinical practice Guidelines in Oncology for kidney cancer; V2.2022; updated September 8th, 2021.

capmatinib (Tabrecta™)

1. Tabrecta [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. August 2022.
2. Awad MM. Impaired c-Met receptor degradation mediated by MET exon 14 mutations in non-small-cell lung cancer. J Clin Oncol. 2016;34(8):879-881.
3. 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.
4. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V1.2023. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated December 22, 2022.
5. Sabari JK, Montecalvo J, Chen R, et al. PD-L1 expression and response to immunotherapy in patients with MET exon 14-altered non-small cell lung cancers (NSCLC). Oral presentation presented at: American Society of Clinical Oncology (ASCO) Annual Meeting. June 2-6, 2017; Chicago, IL.
6. Drilon A, Clark J, Weiss J, et al. Updated antitumor activity of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. Abstract presented at: IASLC 19th World Conference on Lung Cancer. September 23-26, 2018.
7. Novartis. AMCP Formulary Dossier Version 4.1, Tabrecta (capmatinib). May 2020.
8. Novartis. Capmatinib (Tabrecta) METex14 Metastatic NSCLC Overview. January 2023.

futibatinib (Lytgobi®)

11. Goyal L, Meric-Bernstam F, Hollebeque A, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. J Clin Oncol 2022;40: Abstract 4009.
12. Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau HT, Tran B, Kelley RK, Park JO, Javle M, He Y, Benhadji KA, Goyal L. Futibatinib, an Irreversible FGFR1-4 Inhibitor, in Patients with Advanced Solid Tumors Harboring *FGF*/*FGFR* Aberrations: A Phase I Dose-Expansion Study. Cancer Discov. 2022 Feb;12(2):402-415. doi: 10.1158/2159-8290.CD-21-0697. Epub 2021 Sep 22. PMID: 34551969.
13. Lytgobi. Package insert. Taiho Pharmaceutical Co. Ltd; September 2022.
14. National Comprehensive Cancer Network. Hepatobiliary Cancers (Version 3.2022). NCCN. October 14, 2022. Accessed November 7, 2022. hepatobiliary.pdf (nccn.org)

mobocertinib (Exkivity™)

9. Riely GJ, Neal JW, Camidge DR, et al. Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with egfr exon 20 insertion mutations from a phase I/II trial. Cancer Discov. 2021;11(7):1688-1699.
10. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Non-Small Cell Lung cancer. V6.2021. Updated September 30,2021. Accessed October 6, 2021. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450
11. Hanna NH, Robinson AG, Temin S, et al. Therapy for stage iv non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol. 2021;39(9):1040-1091.
12. Rybrevant [Prescribing Information]. Janssen Pharmaceuticals. Horsham, PA. May 2021.

13. American Cancer Society. Treatment non-small cell lung cancer. Accessed August 23, 2021. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell.html.

pemigatinib (Pemazyre™)

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

pirtobrutinib (Jaypirca™)

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

pralsetinib (Gavreto™)

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

selpercatinib (Retevmo™)

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://wclc2019.iaslc.org/wp-content/uploads/2019/08/WCLC2019-Abstract-Book_web-friendly.pdf. 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.

sotorasib (Lumakras™)

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.

tazemetostat (Tazverik™)

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.

tepotinib (Tepmetko)

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.

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.

adagrasib (Krazati®)	
Policy Name	**Disease state**
sotorasib (Lumakras)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation
avapritinib (Ayvakit™)	
Policy Name	**Disease state**
regorafenib (Stivarga)	Gastrointestinal Stromal Tumors (GIST)
dasatinib (Sprycel)	Gastrointestinal Stromal Tumors (GIST)
ripretinib (Qinlock)	Gastrointestinal Stromal Tumors (GIST)
sunitinib (Sutent)	Gastrointestinal stromal tumors (GIST)
imatinib (Gleevec)	Gastrointestinal stromal tumors (GIST) Systemic mast cell disease (systemic mastocytosis)
midostaurin (Rydapt)	Systemic mast cell disease (aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia)
omalizumab (Xolair)	Systemic mastocytosis
belzutifan (Welireg™)	
Policy Name	**Disease state**
N/A	N/A

capmatinib (Tabrecta™)	
Policy Name	**Disease state**
tepotinib (Tepmetko)	Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping
futibatinib (Lytgobi®)	
Policy Name	**Disease state**
pemigatinib (Pemazyre)	Previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements
mobocertinib (Exkivity™)	
Policy Name	**Disease state**
pemigatinib (Pemazyre™)	
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
pirtobrutinib (Jaypirca™)	
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
pralsetinib (Gavreto™)	
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)	
selpercatinib (Retevmo™)	
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
sotorasib (Lumakras™)	
Policy Name	**Disease state**
sotorasib (Lumakras)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation
tazemetostat (Tazverik™)	
Policy Name	**Disease state**
N/A	N/A
tepotinib (Tepmetko)	
Policy Name	**Disease state**
N/A	N/A

Policy Implementation/Update:

adagrasib (Krazati®)	
Action and Summary of Changes	**Date**
Policy created	11/2022

avapritinib (Ayvakit™)	
Action and Summary of Changes	**Date**
Added new indication of indolent systemic mastocytosis (ISM). Updated supporting evidence, E/I section, references for all indications. Added solid tumors and AML to E/I section. Added related policies section.	05/2023
Addition of new indication advanced systemic mastocytosis (AdvSM) and updated trial information for gastrointestinal stromal tumors (GIST)	10/2021
Policy created	05/2020
belzutifan (Welireg™)	
Action and Summary of Changes	**Date**
Policy created	11/2021
capmatinib (Tabrecta™)	
Action and Summary of Changes	**Date**
Added supporting evidence for regular FDA approval of capmatinib (Tabrecta) for the treatment of adults with metastatic NSCLC with METex14 skipping mutation, updated references, added related policies section.	02/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	08/2020
futibatinib (Lytgobi®)	
Action and Summary of Changes	**Date**
Policy created	02/2023
mobocertinib (Exkivity™)	
Action and Summary of Changes	**Date**
Updated from E/I to not medically necessary following withdrawal from U.S. market	02/2024
Policy created	11/2021
pemigatinib (Pemazyre™)	
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
pirtobrutinib (Jaypirca™)	
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
pralsetinib (Gavreto™)	
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
selpercatinib (Retevmo™)	
Action and Summary of Changes	**Date**

Added 120mg and 360mg tablets to the QL table and updated QL to 60/30. Updated QL for 40mg to 90/30	08/2024
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
sotorasib (Lumakras™)	
Action and Summary of Changes	**Date**
Policy created	11/2022
tazemetostat (Tazverik™)	
Action and Summary of Changes	**Date**
Indication of Follicular Lymphoma reviewed and supporting evidence added to policy	01/2021
Policy created	05/2020
tepotinib (Tepmetko)	
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: UMP280

Description

Fecal microbiota spores, live-brpk (Vowst™) is an orally administered microbiome therapy composed of purified Firmicutes spores.

Length of Authorization

- Initial: One-time fill
- Renewal: None

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
fecal microbiota spores, live-brpk (Vowst)	Reduction of recurrence risk of Clostridioides difficile (C. difficile) infection	Capsule	12 capsules/30 days

Initial Evaluation

I. **Fecal microbiota spores, live-brpk (Vowst)** 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 gastroenterologist or infectious disease specialist; **AND**
   C. A diagnosis of **recurrent Clostridioides difficile infection** when the following are met:
      1. Provider attestation that the member has had two or more prior *recurrent C. difficile* episodes in the past 12 months; **AND**
      2. Member had complete remission of the most recent *C. difficile* infection episode with oral antibiotics (e.g., vancomycin, fidaxomicin); **AND**
      3. Provider attestation that the member does not have active *C. difficile* infection (defined as ≤3 unformed stools for 2 or more consecutive days); **AND**
      4. Member has <u>not</u> received a *C. difficile* prophylaxis therapy (e.g., fecal microbiota transplantation (FMT), fecal microbiota, live-jslm (Rebyota), bezlotoxumab (Zinplava)) within the previous 3 months

II. Fecal microbiota spores, live-brpk (Vowst) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Treatment of active Clostridioides difficile infection
   B. Non-recurrent Clostridioides difficile infection
   C. In combination with other Clostridioides difficile prophylaxis regimens (e.g. FMT, bezolotoxumab, Rebyota)
   D. When used for more than one treatment course per 6 months

Renewal Evaluation

I. N/A

Supporting Evidence

I. Fecal microbiota spores, live-brpk (Vowst) was studied in clinical trials in adult patients. Safety and efficacy of Vowst has not been established in the pediatric population.

II. Diagnosis and management of recurrent C. difficile infection require detailed clinical examination in combination with advanced testing (e.g., stool toxin assay). C. difficile has a high rate of recurrence and is highly contagious if not adequately contained and treated. Given the complexities of diagnosis and treatment of the condition, supervision of treatment by an infectious disease specialist or gastroenterologist (GI) is required.

III. Recurrent C. difficile infection can be defined as the reappearance of C. difficile symptoms within a few days, to up to 12 weeks, after symptom resolution. While there is not a definite definition and time frame for C. difficile recurrence across clinical practice and scientific literature, reappearance of symptoms within 8-12 weeks of symptom resolution is often used within clinical trials assessing C. difficile treatment and recurrence prevention. The majority of clinical trials included in the American College of Gastroenterology (ACG) and the C. Difficile Clinical Guidelines and Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) C. Difficile Clinical Practice Guidelines, used a window between 8 and 12 weeks; however, sustained clinical response and rate of recurrence have been measured out to 24 weeks (6 months) in some trials. Risk factors for recurrent C. difficile infections are antibiotic exposure, older age, recent hospitalization, weakened immune system, and history of C. diff infection. Roughly 1/6 patients will experience a recurrence after an initial infection.

IV. Vowst is an oral microbiome therapy studied in ECOSPOR III, a Phase III, double-blind, randomized placebo-controlled trial with 182 adult patients (18 years and older) with recurrent C. difficile infection that had symptom resolution following standard of care antibiotic treatment with vancomycin or fidaxomicin.

V. Within the ECOSPOR III trial, a qualifying episode of C. difficile was defined as: ≥ 3 unformed stools per day for 2 consecutive days, a positive C. difficile stool toxin assay, C. difficile standard of care (SOC) antibiotic therapy (defined as 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID], and an adequate clinical response following SOC antibiotic therapy, defined as < 3 unformed stools in 24 hours for 2 or more consecutive days. Recurrence was defined as ≥ 3 episodes of C. difficile infection within the previous 12 months inclusive of the current episode. The primary efficacy endpoint was the superiority of Vowst versus placebo in reducing the risk of C. difficile recurrence up to 8 weeks after dosing. Rate of C. difficile recurrence at 8 weeks for Vowst treatment group was 12% (n=11) and that for placebo was 40% (n=37), with relative risk reduction of 0.32 (95% CI, 0.18 to 0.58; p<0.001).

VI. Patients that received human monoclonal antibody C. difficile toxin (e.g., Zinplava) or fecal microbiota transplantation (FMT) within previous 3 months prior to the study were excluded

from the ECOSPOR III trial. The efficacy and safety of concurrent use of Vowst and other C. difficile prophylaxis therapies (e.g., FMT or bezlotoxumab (Zinplava), fecal microbiota, live-jslm (Rebyota) has not been evaluated and remains unknown at this time.

VII. While toxin assay diagnostic testing was used within ECOSPOR III, NAAT, which includes PCR testing, is commonly used in clinical practice within a multistep algorithm and is supported by both ACG Clinical Guidelines and IDSA/SHEA C. Difficile Clinical Practice Guidelines.

VIII. In the ECOSPOR III trial population, the overall adverse events (AE) reported for Vowst were similar to those for placebo. Most common AE for Vowst were gastrointestinal disorders (88%), fatigue (59%), chills (21%), decreased appetite (29%), and infection (20%).

IX. Vowst is an alternative to fecal microbiota, live-jslm (Rebyota), bezlotoxumab (Zinplava), or FMT with expected favorability due to oral administration and purported safety advantage compared to FMT. Rebyota is administered via rectal enema, and bezlotoxumab is administered intravenously. FMT may be administered through colonoscopy, capsule, or enema. Head-to-head trials have not been conducted between different C. difficile prophylaxis treatment options, however indirect comparison between trials suggests similar efficacy of recurrence prevention between agents.

Investigational or Not Medically Necessary Uses

I. Vowst has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Treatment of Clostridioides difficile infection
      i. ECOSPOR III did not review Vowst for safety and efficacy in the setting of treatment of C. difficile infection. Vowst is a microbiome therapy and would not have efficacy in treating an active infection without the use of standard of care antibiotics (e.g., vancomycin and fidaxomicin).
   B. Non-recurrent Clostridioides difficile infection
      i. Safety and efficacy have not been established for Vowst for non-recurrent C. difficile. ACG C. difficile guidelines and IDSA/SHEA C. difficile guidelines recommends FMT and Zinplava only for recurrent C. difficile infection, and not for primary prevention of C. difficile infection.
   C. In combination with other Clostridioides difficile regimens (e.g., FMT, bezlotoxumab, Rebyota)
      i. There is lack of safety and efficacy data when C. difficile prophylaxis regimens are used concurrently. Clinical trials evaluating C. difficile prophylaxis treatments (PUNCH CD3 for Rebyota, Modify I and II for bezlotoxumab (Zinplava), ECOSPOR III and IV for Vowst) excluded patients that had been previously treated (within 3 months of study enrollment), or planned to concurrently use other C. difficile prophylaxis treatment options, including fecal microbiota transplant. The safety profile of combination therapy is unknown at this time with potential safety concerns. Additionally, efficacy of combination has not been established in any clinical trials to date or real-world data.
   D. When used for more than one treatment course per 6 months

i. Repeat dosing of Vowst was not studied in ECOSPOR III. In the open-label extension trial, ECOSPOR IV, there were only 4 patients that had repeat dosing of Vowst after having C. difficile recurrence within 8 weeks that were previously enrolled in ECOSPOR III. Additionally, rates of recurrence beyond six months or safety and efficacy of retreatment with Vowst has not been established. Due to lack of adequate safety and efficacy data to establish an appropriate timeline for retreatment, retreatment with Vowst within 6 months will not be allowed.

References

1) Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection. *N Engl J Med*. 2022; 386(3):220-229.
2) McGovern BH, Ford CB, Henn MR, et al. SER-109, an Investigational Microbiome Drug to Reduce Recurrence After *Clostridioides difficile* Infection: Lessons Learned From a Phase 2 Trial. *Clin Infect Dis*. 2021;72(12):2132-2140.
3) Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults, *Clin Infect Dis*. 2021; 73(5): e1029–e1044.
4) Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. Am. J. Gastroenterol. 2021; 116 (6): 1124-1147.
Seres Therapeutics, Inc. ECOSPOR IV: An Open-Label Extension of Study SERES-012 and Open-Label Program for Evaluating SER-109 in Subjects With Recurrent Clostridioides Difficile Infection (RCDI). clinicaltrials.gov. Published May 24, 2022. Accessed December 5, 2022. https://clinicaltrials.gov/ct2/show/NCT03183141.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	2/2023

fedratinib (Inrebic®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP083

Split Fill Management*

Description

Fedratinib (Inrebic) is an orally administered kinase inhibitor with activity against both wild-type and mutated Janus-associated kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
fedratinib (Inrebic)	Intermediate- or high-risk myelofibrosis	100 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Fedratinib (Inrebic)** 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 (MF)** when the following are met:
      1. Splenomegaly is present and baseline spleen volume is documented; **AND**
      2. Documentation of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain); **AND**
      3. Platelet count, measured within the past 30 days, is greater than or equal to, 50 x 10^9/L; **AND**
      4. Treatment with ruxolitinib (Jakafi) has been ineffective or not tolerated.

II. Fedratinib (Inrebic) is considered investigational when used for all other conditions, including but not limited to:
   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

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ArrayRx administered by moda HEALTH

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 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), and 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. Fedratinib (Inrebic) and ruxolitinib (Jakafi) are approved for MF when platelet count is ≥ 50 x 10^9/L. These medications 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). These therapies have only 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. Fedratinib (Inrebic) was evaluated as an initial treatment in patients with intermediate-2 or high-risk MF (JAKARTA) and as a second-line treatment in patients who are ruxolitinib (Jakafi) resistant or intolerant (JAKARTA-2).
    - JAKARTA: Phase 3, double-blind, randomized, placebo-controlled trial with 289 total patients. The primary and secondary endpoints were superior to placebo: spleen volume reduction of 35% and at least a 50% reduction in total symptom score.
    - JAKARTA-2: Single-arm, open-label, non-randomized, Phase 2 trial in ruxolitinib (Jakafi) resistant or intolerant patients, which showed patients were able to achieve spleen volume reduction of 35% as well as a 50% or greater reduction in TSS.
    - Dose interruptions due to adverse events occurred in 21% of patients, dose reductions in 19%, and permanent discontinuation in 14%. Split-fill is applied.

IV. As of February 2022, NCCN guidelines recommend treatment with fedratinib (Inrebic) or ruxolitinib (Jakafi) in higher risk MF when platelet count is greater than 50 x 10^9/L (Category 1).

V. Fedratinib (Inrebic) has shown to reduce spleen size and improve disease-related symptoms; however, reduction of spleen volume alone without associated improvement in symptoms has unknown clinical value. Therapy should be initiated in presence of disease-related symptoms in those that are not candidates for transplant, and it is appropriate to continue treatment when therapy has stabilized or improved symptoms.

VI. Fedratinib (Inrebic) uniquely carries a black box warning for encephalopathy including Wernicke's, due to seven cases of Wernicke's encephalopathy during clinical trials. Providers should monitor patients for risk prior to starting fedratinib (Inrebic) and during therapy. In patients that have elevated risk or develop encephalopathy on treatment, alternative JAK inhibitors may be considered for use.

VII. There is no evidence of superiority for any of the three JAK inhibitors for MF; however, when balancing safety and cost effectiveness, use of ruxolitinib (Jakafi) prior to coverage consideration of fedratinib (Inrebic) is required.

Investigational or Not Medically Necessary Uses

I. Fedratinib (Inrebic) 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 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

** 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. Inrebic [Prescribing Information]. Celgene Corporation: Summit, NJ. August 2019. Revised 12/2021
2. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf Updated February 28, 2022
3. UpToDate, Inc Management of primary myelofibrosis. UpToDate [database online]. Waltham, MA. Last updated Dec 06, 2021.Available at: http://www.uptodate.com/home/index.html.

4. Celgene Corporation [online press release]. U.S. FDA Approves INREBIC® (Fedratinib) as First New Treatment in Nearly a Decade for Patients with Myelofibrosis. Available at: https://ir.celgene.com/press-releases/press-release-details/2019/US-FDA-Approves-INREBIC-Fedratinib-as-First-New-Treatment-in-Nearly-a-Decade-for-Patients-With-Myelofibrosis/default.aspx. Updated August 16, 2019.
5. Jakafi [Prescribing Information]. Incyte Corporation: Wilmington, DE. May 2019, Revised 9/2021.
6. Pardanani A, Harrison C, Cortes JE, et al. Safety and Efficacy of Fedratinib in Patients with Primary or Secondary Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2015;1(5):643-51.
7. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. Lancet Haematol. 2017;4(7):e317-e324.
8. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.
9. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: An updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. Am J Hematol. 2020 Jun;95(6):594-603. doi: 10.1002/ajh.25777. Epub 2020 Apr 17. PMID: 32129512; PMCID: PMC7317815.
10. Vonjo [Prescribing Information]. CTI Biopharma Corp. Seattle, WA. February 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
ruxolitinib (Jakafi)	Intermediate- or high-risk myelofibrosis
	Polycythemia vera
	Graft versus-host disease (acute or chronic)
pacritinib (Vonjo)	Intermediate- or high-risk myelofibrosis

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to new formatting changes including addition of related policy. Reviewed for new indications and appropriateness of policy criteria. Updated supporting evidence. Simplified required diagnosis, to "Int. or high risk MF". Added an age edit to align with the labeled indication/age and known safety profile (i.e., adults). Added requirement of both: splenomegaly AND disease related symptoms. Added requirement of prior ruxolitinib (Jakafi) treatment. Updated renewal criteria to remove requirement of SVR reduction.	5/2022
Criteria created	9/2019

fenfluramine (Fintepla®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP203

Description

Fenfluramine (Fintepla) is an orally administered amphetamine derivative serotonin 5HT-2 receptor agonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
fenfluramine (Fintepla)	Dravet Syndrome	2.2 mg/ml solution	360 ml/30 days Monthly quantity (in mL) to allow for a maximum of 26 mg (12 mL) per day
	Lennox-Gastaut Syndrome		

**The maximum daily dose differs with concomitant stiripentol and clobazam with a maximum daily dose of 17 mg (7.7mL) per day.*

Initial Evaluation

I. **Fenfluramine (Fintepla)** may be considered medically necessary when the following criteria are met:
   A. Member is two years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of baseline seizure frequency and severity**; AND**
   D. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
   E. Provider attestation fenfluramine (Fintepla) will not be used in combination with cannabidiol (Epidiolex); **AND**
   F. A diagnosis of one of the following:
      1. **Dravet syndrome; AND**:
         i. <u>All</u> of the following have been ineffective, not tolerated or are contraindicated (‡ Please note: These agents may be subject to prior authorization and may require an additional review):
            a. valproate
            b. clobazam
            c. cannabidiol (Epidiolex)‡
            d. stiripentol (Diacomit)‡; **OR**

2. **Lennox-Gastaut Syndrome**; **AND**
    i. Two of the following have been ineffective, not tolerated or all are contraindicated (‡ Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
        a. valproate
        b. lamotrigine
        c. rufinamide‡
        d. clobazam
        e. felbamate
        f. topiramate**; AND**
    ii. Treatment with cannabidiol (Epidiolex)‡ has been ineffective, not tolerated or contraindicated

II. Fenfluramine (Fintepla) is considered investigational when used for all other conditions, including but not limited to:
    A. Epileptic encephalopathies associated with SCN1A mutations
    B. Seizure disorders other than Dravet syndrome and Lennox-Gastaut syndrome
    C. Use in combination with cannabidiol (Epidiolex)

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 fenfluramine (Fintepla) will not be used in combination with cannabidiol (Epidiolex)**; AND**
IV. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
V. Provider attests member has exhibited improvement or stability of disease symptoms (e.g., reduction in seizure frequency).

Supporting Evidence

I. Fenfluramine (Fintepla) is FDA-approved for use in Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) for patients aged two years and older. Fenfluramine was originally introduced as a weight-loss agent at higher doses and was pulled from the market due to reports of cardiovascular adverse events (i.e., valvular heart disease and pulmonary arterial hypertension). Given the serious adverse safety profile of fenfluramine (Fintepla), and lack of evaluation in patients under two years of age, use outside of the FDA-approved two years of age and older is not recommended.

II. Both Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are associated with treatment-resistant seizures of multiple types, neurodevelopmental delay, and profound cognitive impairment. Despite the use of numerous antiseizure medications (ASMs) in these conditions, ASMs tend to have limited efficacy. Due to these conditions being treatment refractory, high-touch care and monitoring required, fenfluramine (Fintepla) must be prescribed by, or in consultation with a neurologist.

III. Fenfluramine (Fintepla) may be used as monotherapy, concomitantly with stiripentol (Diacomit), or concomitantly as triple-therapy with stiripentol (Diacomit) and clobazam (in DS). However, concomitant use with cannabidiol (Epidiolex) has not been studied in DS nor LGS. The efficacy and safety of fenfluramine (Fintepla) used in combination with cannabidiol (Epidiolex) remains unknown.

IV. Dravet syndrome:

- Dravet syndrome is a rare pediatric genetic epilepsy syndrome characterized by refractory epilepsy and neurodevelopmental problems starting in infancy. Dravet syndrome is commonly misdiagnosed as other conditions such as cerebral palsy, Lennox-Gastaut syndrome, or vaccine encephalopathy.
- Fenfluramine (Fintepla) was studied in two randomized, double-blind, placebo-controlled Phase 3 trials in 206 patients aged two to 18 years with Dravet syndrome, where convulsive seizures were not completely controlled by current AED therapy.
- Trial one (Lagae L, et al. 2019) was a Phase 3, randomized, double-blind, placebo-controlled, multicohort, multi-country trial that studied 119 patients ages two to 18 years, who had at least four convulsive seizures in a four-week period for the past 12 weeks prior to screening and were stable for at least four weeks prior to screening and throughout the trial on valproate, clobazam, topiramate, or levetiracetam. This trial excluded patients who were on concomitant stiripentol (Diacomit) therapy. Patients were randomized 1:1:1 to either fenfluramine (Fintepla) 0.7 mg/kg/day, fenfluramine (Fintepla) 0.2 mg/kg/day, or matching placebo twice daily. Patients in the trial had a mean baseline convulsive seizure frequency of 40.3 per 28 days and a mean baseline of 2.4 concomitant AEDs. The primary efficacy outcome was the reduction in mean monthly convulsive seizure frequency (MCSF) over the 14-week treatment period with fenfluramine (Fintepla) 0.7 mg/kg/day versus placebo. A key secondary endpoint was the reduction in MCSF over the 14-week treatment period with fenfluramine 0.2 mg/kg/day versus placebo. The primary end point result was a 62.3% (95% Cl -47.7 to -72.8) greater reduction in mean MCSF over the 14-week treatment period with fenfluramine 0.7 mg/kg/day versus placebo ($p<0.0001$). The key secondary endpoint result was a 32.4% (95% Cl -6.2 to -51.3) greater reduction in mean MCSF over the 14-week treatment period with fenfluramine (Fintepla) 0.2 mg/kg/day versus placebo ($p=0.0209$).
- Trial two (Nabbout R, et al. 2019) was a Phase 3, randomized, double-blind, placebo-controlled, multi-country trial that studied 87 patients ages two to 18 years, who were receiving concomitant stiripentol (Diacomit), valproate, clobazam, levetiracetam, or topiramate, and who had a stable baseline with six or more convulsive seizures during the six-week baseline, with two or more seizures in the first three weeks and two or more seizures in the second three weeks. Less than 10% of the subjects were reported to have received one of the following

concomitant AED's: acetazolamide, clonazepam, diazepam, ethosuximide, felbamate, gamma-aminobutyric acid, lorazepam, phenobarbital, pregabalin, or zonisamide. Patients were randomized 1:1 to either fenfluramine (Fintepla) 0.4 mg/kg/day or matching placebo twice daily. Patients in the trial had a mean baseline convulsive seizure frequency of 14 versus 10.7 in the fenfluramine (Fintepla) versus placebo arm. The primary efficacy outcome was the difference between fenfluramine (Fintepla) and placebo on the change in mean MCSF from baseline to the 15-week combined titration and maintenance (T+M) periods. A key secondary endpoint was the proportion achieving 50% or greater reduction from baseline levels in MCSF. The primary endpoint was 54% (95% CI, 35.6%-67.2%) achieved greater reduction in mean MCSF between the baseline and T + M periods with fenfluramine versus placebo ($p<0.001$). Results of the key secondary endpoint of reduction in mean MCSF in the fenfluramine group, 23 of 43 (54%) versus the placebo group, two of 44 (5%) ($p <0.001$).

- The NICE guidelines for Dravet syndrome, recommend valproate as first-line therapy, then clobazam, cannabidiol (Epidiolex), and stiripentol (Diacomit) as second-line therapy. These guidelines have not been updated to include fenfluramine (Fintepla). 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).
- Based on the established safety, efficacy, and cost effectiveness of valproate, clobazam, cannabidiol (Epidiolex), and stiripentol (Diacomit) relative to fenfluramine (Fintepla), trial of two generics, cannabidiol (Epidiolex), and stiripentol (Diacomit) is required before approval of fenfluramine (Fintepla).

V. Lennox-Gastaut syndrome:

- Lennox-Gastaut syndrome is associated with severe seizures in childhood that typically present before eight years of age. There are a variety of causes including cortical malformations, tumors, neurocutaneous syndromes (i.e., tuberous sclerosis complex), encephalopathies, meningitis, and head injuries.
- Fenfluramine (Fintepla) was studied in a Phase 3 randomized, double-blind, placebo-controlled trial in 263 patients aged two to 35 years with Lennox-Gastaut syndrome who were using stable antiseizure regimens. Patients were eligible to enroll if they had: onset of seizures at age 11 years or younger, multiple seizure types including tonic or atonic, stable 4-week seizure baseline with 2 or more drop seizures per week, abnormal cognitive development, and medication history showing electroencephalogram evidence of abnormal background activity with slow spike-and-wave pattern. The trial excluded patients with degenerative neurological disease, history of hemiclonic seizures in the first year of life, only drop seizure clusters, and previous or current cardiovascular abnormalities. Patients were randomized 1:1:1 into fenfluramine (Fintepla) 0.7 mg/kg/day, 0.2 mg/kg/day or placebo stratified by weight less than 37.5 kg or greater than 37.5. The population characteristics included: median age of 13 years (range 2-35 years), median drop seizure frequency per 28 days 85 in 0.7 mg/kg/day, 83 in 0.2 mg/kg/day, and 53 in placebo. A mean previous antiseizure medication use of 7-8 medications. Concomitant seizure medications >20% included valproate, clobazam, lamotrigine,

rufinamide and levetiracetam. The primary efficacy outcome was the percentage change from baseline in drop seizure frequency for patients in the 0.7 mg/kg/day compared to placebo. The secondary efficacy endpoints were percentage change from baseline in frequency of drop seizures in the 0.2 mg/kg/day group, a 50% or greater response rate, and the proportion of patients who achieved improvement on the Clinical Global Impressions-Improvement (CGI-I) scale. The study met the primary efficacy endpoint, patients who received 0.7 mg/kg/day achieved a statistically significant median difference in drop seizure frequency of -19.9% (95% CI, -31 to -8.7, P=.001) compared to placebo. The study achieved statistically significant results in the secondary endpoint of 50% or greater reduction in drop seizure frequency, with 25% (P=.02) achieving greater than 50% reduction in the 0.7 mg/kg/day and 28% (P=.005) in the 0.2 mg/kg/day groups compared to 10% in placebo. Additionally, 26% (P=.001) of patients in 0.7 mg/kg/day group had a clinically meaningful improvement in CGI-I of much improved or very much improved compared to 20% in the 0.2 mg/kg/day group and 6% in placebo.

- The American Epilepsy Society guidelines for Lennox-Gastaut syndrome, recommend use of lamotrigine, topiramate, felbamate with clobazam, and rufinamide as add-on therapy, they do not make recommendations for sequential therapy. The NICE guidelines for LGS recommend use of valproate as well as lamotrigine, cannabidiol (Epidiolex), clobazam, rufinamide, topiramate, and felbamate (though not licensed for use in the UK).
- Based on the established safety, efficacy, and cost effectiveness of valproate, lamotrigine, rufinamide**,** clobazam, felbamate, topiramate, and cannabidiol (Epidiolex) relative to fenfluramine (Fintepla), trial of two generic agents and cannabidiol (Epidiolex) is required before approval of fenfluramine (Fintepla).

VI. Fenfluramine (Fintepla) is a Schedule IV controlled substance that is only available through a restricted program called the Fintepla REMS. Fenfluramine (Fintepla) carries a black-box warning for valvular heart disease (VHD) and pulmonary arterial hypertension (PAH). Echocardiogram assessments are required before, during, and after treatment with fenfluramine (Fintepla).

Investigational or Not Medically Necessary Uses

I. Fenfluramine (Fintepla) 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. Seizure disorders other than Dravet syndrome and Lennox-Gastaut syndrome

Appendix

I. Table 1: fenfluramine (Fintepla) Recommended Titration Schedule

	Without concomitant stiripentol		**With concomitant stiripentol and clobazam**	
	Weight-based Dosage	**Maximum Total Daily Dosage**	**Weight-based Dosage**	**Maximum Total Daily Dosage**

Initial Dosage	0.1 mg/kg twice daily	26 mg	0.1 mg/kg twice daily	17 mg
Day 7	0.2 mg/kg twice daily	26 mg	0.15 mg/kg twice daily	17 mg
Day 14	0.35 mg/kg twice daily	26 mg	0.2 mg/kg twice daily	17 mg

References

1. Fintepla [Prescribing Information]. Zogenix, Inc: Emeryville, CA. March 2022.
2. Andrade DM, Nascimento FA, Nordli DR et al. (2020). Dravet syndrome: management and prognosis. UpToDate. Retrieved July 20, 2020, from: https://www-uptodate-com.liboff.ohsu.edu/contents/dravet-syndrome-management-and-prognosis
3. Sullivan J, Knupp K, Wirrell E et al. (2018). Dravet syndrome. National Organization for Rare Disorders. Retrieved July 22, 2020, from: https://rarediseases.org/rare-diseases/dravet-syndrome-spectrum/
4. (2014). Dravet syndrome. Orphanet. Retrieved July 22, 2020, from: https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=33069&lng=EN
5. Shafer PO, Kiriakopoulos E, Wirrell E (2019). Dravet syndrome. Epilepsy Foundation. Retrieved July 22, 2020, from: https://www.epilepsy.com/learn/types-epilepsy-syndromes/dravet-syndrome
6. Wirrel EC, Laux L, Donner E et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American Consensus Panel. Pediatric Neurology 2017;68:18-34. Available from: https://www.pedneur.com/article/S0887-8994(16)31037-2/pdf
7. Lagae L, Sullivan J, Knupp K et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet 2020;394(10216):2243-2254. Available from: https://pubmed-ncbi-nlm-nih-gov.liboff.ohsu.edu/31862249/
8. Nabbout R, Mistry A, Zuberi S et al. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. JAMA Neurol 2019;77(3):300-308. Available from: https://pubmed-ncbi-nlm-nih-gov.liboff.ohsu.edu/31790543/
9. Wilfong A, Nordli DR et al. (2022). Epilepsy syndrome in children. UpToDate. Retrieved June 17,2022, from: https://www.uptodate.com/contents/epilepsy-syndromes-in-children
10. Lennox-gastaut syndrome. NORD (National Organization for Rare Disorders).
11. Knupp KG, Scheffer IE, Ceulemans B, et al. Efficacy and safety of fenfluramine for the treatment of seizures associated with lennox-gastaut syndrome: a randomized clinical trial. JAMA Neurol. Published online May 2, 2022.
12. Arzimanoglou A, French J, Blume WT, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol. 2009;8(1):82-93.
13. 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.
14. Chin RF, Mingorance A, Ruban-Fell B, et al. Treatment guidelines for rare, early-onset, treatment-resistant epileptic conditions: a literature review on dravet syndrome, lennox-gastaut syndrome and cdkl5 deficiency disorder. Front Neurol. 2021;0.
15. Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs: 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(2):82-90.
16. National Instituite for Health and Care Excellence. Fenfluramine for treating seizures associated with dravet syndrome. Nice.org.uk. July 8, 2022. Accessed July 25, 2022. https://www.nice.org.uk/guidance/ta808

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

stiripentol (Diacomit)	Dravet syndrome
vigabatrin (Sabril, Vigadrone)	Refractory complex partial epileptic seizure, adjunct therapy West syndrome (infantile spasms)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication (Lennox-Gastaut syndrome), added weight-based dosing to QL for Dravet syndrome, updated initial and renewal evaluation criteria (Dravet syndrome), updated supporting evidence, added related policies table.	08/2022
Policy created	11/2020

Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®)
UMP POLICY

Policy Type: PA Pharmacy Coverage Policy: UMP185

Description
Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®) is an opioid agonist FDA approved for the treatment of breakthrough cancer pain in those who are tolerant to, or already receiving, constant opioid treatment for continual cancer pain.

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

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
fentanyl citrate (Abstral)	100 mcg sublingual tablet	Chronic pain associated with cancer	120 tablets/30 days
	200 mcg sublingual tablet		120 tablets/30 days
	300 mcg sublingual tablet		120 tablets/30 days
	400 mcg sublingual tablet		120 tablets/30 days
	600 mcg sublingual tablet		120 tablets/30 days
	800 mcg sublingual tablet		120 tablets/30 days
fentanyl citrate (Actiq)	200 mcg lozenge handle	Chronic pain associated with cancer	120 lozenges/30 days
	400 mcg lozenge handle		120 lozenges/30 days
	600 mcg lozenge handle		120 lozenges/30 days
	800 mcg lozenge handle		120 lozenges/30 days
	1200 mcg lozenge handle		120 lozenges/30 days
	1600 mcg lozenge handle		120 lozenges/30 days
fentanyl citrate (Fentora)	100 mcg buccal tablet	Chronic pain associated with cancer	120 tablets/30 days
	200 mcg buccal tablet		120 tablets/30 days
	400 mcg buccal tablet		120 tablets/30 days
	600 mcg buccal tablet		120 tablets/30 days
	800 mcg buccal tablet		120 tablets/30 days
fentanyl citrate (Lazanda)	100 mcg nasal spray	Chronic pain associated with cancer	15 bottles/30 days
	400 mcg nasal spray		15 bottles/30 days
fentanyl citrate (Subsys)	100 mcg sublingual spray	Chronic pain associated with cancer	4 cartons/30 days
	200 mcg sublingual spray		4 cartons/30 days
	400 mcg sublingual spray		4 cartons/30 days
	600 mcg sublingual spray		4 cartons/30 days
	800 mcg sublingual spray		4 cartons/30 days
	1200 mcg sublingual spray		4 cartons/30 days
	1600 mcg sublingual spray		4 cartons/30 days
fentanyl citrate (fentanyl citrate)	200 mcg lozenge handle	Chronic pain associated with cancer	120 lozenges/30 days
	400 mcg lozenge handle		120 lozenges/30 days
	600 mcg lozenge handle		120 lozenges/30 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

	800 mcg lozenge handle		120 lozenges/30 days
	1200 mcg lozenge handle		120 lozenges/30 days
	1600 mcg lozenge handle		120 lozenges/30 days

Initial Evaluation

I. Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) may be considered medically necessary when the following criteria are met:
   A. Member has a diagnosis of **chronic pain associated with cancer**; **AND**
   B. Member is enrolled into the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program**; AND**
   C. Member is 18 years of age or older; **OR**
      1. If request is for fentanyl citrate (Actiq), member is 16 years of age or older; **AND**
   D. Medication is prescribed by, or in consultation with, an oncologist or pain specialist; **AND**
   E. Member is opioid tolerant; **AND**
   F. Member is currently experiencing breakthrough cancer pain, for which fentanyl citrate is being prescribed to treat; **AND**
   G. The provider has recorded baseline and ongoing assessments of measurable, objective pain scores and function scores. These should be tracked serially in order to demonstrate clinically meaningful improvements in pain and function; **AND**
   H. The patient has been screened for mental health disorders, substance use disorder, naloxone use; **AND**
   I. The provider has checked the Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives

II. Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Non-tolerant opioid members
   B. Any indication that is not for treatment of breakthrough pain in patients experiencing chronic pain associated with cancer

Renewal Evaluation

I. See initial evaluation section.

Supporting Evidence

I. Based off clinical trials, there is currently no evidence to support the use of fentanyl citrate (Abstral®, Fentora®, Lazanda®, Subsys®) in any age group below 18 years of age, with the exception of fentanyl citrate (Actiq®, fentanyl citrate) which was studied in those aged 16 years and older.

II. Due to the FDA indication, Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS), and strict dosing guidelines, these agents are not to be prescribed without the consultation or direct supervision of a pain specialist or oncologist.
III. All fentanyl citrate products, and the parties involved in their use (i.e., outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors) are required to be enrolled into the TIRF REMS program, in accordance with FDA guidelines.
IV. The policy aligns with recommendations of the Centers for Disease Control, the Washington State Agency Medical Directors Group, and the Bree Collaborative around safe and appropriate opioid prescribing.
V. This policy is in full compliance with UMP's regulations and mandates regarding the chronic use of opioids.
VI. This policy applies to all groups under UMP, including Public Employees Benefit Board (PEBB) and School Employees Benefits Board (SEBB).

Investigational or Not Medically Necessary Uses

I. Fentanyl citrate (Abstral) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines dental pain, or use in the emergency department
II. Fentanyl citrate (Actiq)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines and dental pain
III. Fentanyl citrate (Fentora)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain, including headache/migraine and dental pain
IV. fentanyl citrate (Lazanda)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department
V. fentanyl citrate (Subsys)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department

Appendix

I. Table 1: Product dosing schedule and conversion from lozenge (Actiq) to other formulation

Product Name	Titration Dosing Schedule
fentanyl citrate (Abstral)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half

	hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Abstral*	
	200mcg	2x 100mcg, *or* 1x 200mg tab
	300mcg	3x 100mcg, *or* 1x 300mg tab
	400mcg	4x 100mcg, *or* 2x 200mcg, *or* 1x 400mg tab
	600mcg	3x 200mcg, *or* 1x 600mg tab
	800 mcg	4x 200mcg, *or* 1x 800mg tab
Initial Dosing Recommendations for Patients on ACTIQ		
Current ACTIQ Dose (mcg)		**Initial Abstral Dose (mcg)**
200		100 mcg
400		200 mcg
600		200 mcg
800		200 mcg
1200		200 mcg
1600		400 mcg
Product Name		**Titration Dosing Schedule**
fentanyl citrate (Actiq)	**Start:** 200mcg taken over 15 minutes, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 200mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.*	
	400 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	600 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	800 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	1200 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	1600 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
Product Name		**Titration Dosing Schedule**

fentanyl citrate (Fentora)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Fentora.*	
	200 mcg buccal tablet 2x 100mcg, *or*	1x 200mg tab
	400 mcg buccal tablet	4x 100mcg, *or* 2x 200mg tab, *or* *1x 400mg tab*
	600 mcg buccal tablet	3x 200mcg, *or* 1x 600mg tab
	800 mcg buccal tablet	4x 200mcg, *or* 1x 800mg tab
Initial Dosing Recommendations for Patients on ACTIQ		
Current ACTIQ Dose (mcg)		**Initial Fentora Dose (mcg)**
200		100 mcg
400		100 mcg
600		200 mcg
800		200 mcg
1200		2x 200 mcg
1600		2x 200 mcg
For patients converting from ACTIQ doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg FENTORA tablet and should proceed using multiples of this tablet strength		
Product Name		**Titration Dosing Schedule**
fentanyl citrate (Lazanda)	**Start:** 100mcg (one spray in each nostril) if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Due to differences in pharmacokinetic properties and individual variability, do not switch patients on a mcg per mcg basis from any other fentanyl product to Lazanda as Lazanda is not equivalent with any other fentanyl product, nor is Lazanda a generic version of any other fentanyl product.*	
	200 mcg nasal spray *Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg*	2 x 100 mcg spray (1 in each nostril)
	400 mcg nasal spray	1 x 400 mcg
	800 mcg nasal spray *Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg*	2 x 400mcg (1 in each nostril)
Product Name		**Titration Dosing Schedule**

fentanyl citrate (Subsys)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Subsys.*	
	100 mcg sublingual spray	1 × 100 mcg unit
	200 mcg sublingual spray	1 × 200 mcg unit
	400 mcg sublingual spray	1 × 400 mcg unit
	600 mcg sublingual spray	1 × 600 mcg unit
	800 mcg sublingual spray	1 × 800 mcg unit
	1200 mcg sublingual spray	2 × 600 mcg unit
	1600 mcg sublingual spray	2 × 800 mcg unit

Initial Dosing Recommendations for Patients on ACTIQ	
Current ACTIQ Dose (mcg)	**Initial Subsys Dose (mcg)**
200	100 mcg
400	100 mcg
600	200 mcg
800	200 mcg
1200	400 mcg
1600	400 mcg

a. For patients converting from Actiq doses 400 mcg and below, titration should be initiated with 100 mcg SUBSYS and should proceed using multiples of this strength.
b. For patients converting from Actiq doses of 600 and 800 mcg, titration should be initiated with 200 mcg SUBSYS and should proceed using multiples of this strength.
c. For patients converting from Actiq doses of 1200 and 1600 mcg, titration should be initiated with 400 mcg SUBSYS and should proceed using multiples of this strength

Product Name	**Titration Dosing Schedule**	
fentanyl citrate (fentanyl citrate)	**Start:** 200mcg taken over 15 minutes, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 200mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.*	
	200 mcg lozenge handle	1 × 200 mcg unit
	400 mcg lozenge handle	1 × 400 mcg unit
	600 mcg lozenge handle	1 × 600 mcg unit
	800 mcg lozenge handle	1 × 800 mcg unit
	1200 mcg lozenge handle	1 × 1200 mcg unit
	1600 mcg lozenge handle	2 × 1600 mcg unit

References

1. Abstral® [Prescribing Information]. Solana Beach, CA: Sentynl Therapeutics, Inc. October 2019.
2. Actiq® [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA, Inc. October 2019.
3. Fentora® [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA, Inc. October 2019.
4. Lazanda® [Prescribing Information]. Northbrook, IL: West Therapeutic Development, LLC October 2019.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

5. Subsys® [Prescribing Information]. Chandler, AZ: Insys Therapeutics, Inc. October 2019.
6. Washington State Agency Medical Directors Group. Interagency Guideline on Prescribing Opioids for Pain. 3rd Edition, June 2015. Available: www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed attestation criteria following UMP guidance, as cancer is exempt diagnosis for the attestation requirement. Per UMP guidance, left in baseline and ongoing pain assessments, mental health and substance abuse screening, and provider check of Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives.	06/2020
Converted to policy, added in REMS question, age limitation question, and clarified prescribing provider specialty needed for approval.	04/2020
Previous reviews	11/15/13, 12/28/17
Criteria created	12/2011

fitusiran (Qfitlia™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP321

Description

Fitusiran (Qfitlia) is a subcutaneous small interfering RNA.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
fitusiran (Qfitlia)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent (≥12 years old) patients with hemophilia A or B with or without inhibitors	50mg/0.5mL prefilled pen	**Initial:** 0.5mL/56 days **Renewal**: See appendix
		20mg/0.2mL vial	See appendix

Initial Evaluation

I. **Fitusiran (Qfitlia)** 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 hematologist; **AND**
   C. Medication will not be used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
   D. Fitusiran (Qfitlia) will be used as routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
   E. A diagnosis of one of the following:
      1. **Hemophilia A with inhibitors**; **AND**
         i. Clinical documentation confirming of a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units)]; **AND**
         ii. Member has had two or more documented episodes of spontaneous bleeding; **AND**
         iii. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**
      2. **Hemophilia A without inhibitors**; **AND**
         i. Clinical documentation confirming that the member does not have a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units); **AND**
         ii. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
            a. Member has had two or more documented episodes of spontaneous bleeding; **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

iii. Clinical documentation that prior prophylaxis with factor VIII (e.g., Advate, Eloctate, Nuwiq, etc.) was ineffective for prevention of bleeding episodes; **AND**

iv. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**

3. Hemophilia B with inhibitors; AND

i. Clinical documentation confirming of a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units)]; **AND**

ii. Member has had two or more documented episodes of spontaneous bleeding; **OR**

a. Member has had an inadequate response to Immune Tolerance Induction (ITI); **OR**

4. Hemophilia B without inhibitors; AND

i. Clinical documentation confirming that the member does not have a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units); **AND**

ii. Member has moderate to severe hemophilia B (defined as factor IX level of less than or equal to 5%); **OR**

a. Member has had two or more documented episode of spontaneous bleeding; **AND**

iii. Clinical documentation that prior prophylaxis with factor IX (e.g., BeneFIX, Idelvion, etc.) was ineffective for the prevention of bleeding episodes

II. Fitusiran (Brand) is considered investigational when used for all other conditions, including but not limited to:

A. Fitusiran (Qfitlia) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]

B. Pediatric patients <12 years of age with hemophilia A or B

C. Von Willebrand 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 (e.g., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**

IV. Medication will not be used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**

V. Documentation of antithrombin (AT) lab value within the past three months; **AND**

A. If member has been established on a dose of 10mg administered once every two months, most recent antithrombin (AT) is above 15%

Supporting Evidence

I. Fitusiran (Qfitlia) is a novel synthetic small interfering RNA (siRNA) FDA-approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent (≥12 years old) patients with hemophilia A or B with or without inhibitors. Fitusiran (Qfitlia) is a subcutaneous injection dosed monthly or every other month. Fitusiran (Qfitlia) targets the production of antithrombin (AT) which serves as up to 80% of the inhibitory component to thrombin formation. When antithrombin levels are reduced, the clotting cascade can continue to function leading to hemostasis.

II. The efficacy and safety of fitusiran (Qfitlia) has not been studied in a pediatric population less than 12 years of age. Current FDA approval is limited to those 12 years of age and older.

III. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX) are X-linked inherited coagulation factor deficiencies that result in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A and B. The severity of an individual's hemophilia is determined by the amount of clotting factor present. Plasma levels of FVIII or FIX < 40% are indicative of hemophilia; however, hemophilia A and B are classified moderate when factor levels are 1% to < 5%, and severe when factor levels are < 1%. Joint bleeds are the most frequent bleeding experienced by people with hemophilia of all severities (70-80%) which can lead to deformity, arthropathy, and irreversible joint damage leading to decreased mobility. Given the complexities of diagnosis and treatment of hemophilia A and B, supervision of treatment by a hematologist is required.

IV. Typical hemophilia therapies include factor replacement with clotting factor concentrates (CFCs). For some patients treated with CFCs, neutralizing antibodies (i.e., inhibitors) develop in response to repeated exposure to exogenous factor products. Inhibitors are most commonly developed in patients with severe hemophilia A (30%). Incidence of inhibitor development in mild and moderate hemophilia A and hemophilia B populations are lower at 5% and 3% respectively. Inhibitors can significantly increase the cost of care and make bleeding episodes more difficult to treat as high doses of CFCs or bypassing agents are needed to circumvent inhibitors.

V. The World Federation of Hemophilia (WFH) guidelines recommend use of agents for both bleeding prophylaxis and control of acute breakthrough bleeds. Therapy recommendations are not sequential but rather cite the need for individualized care considering a patient's bleeding phenotype, joint status, pharmacokinetic profile, and preference. Medications include factor replacement with clotting factor concentrates (CFCs) (i.e., standard half-life (SHLs) for FVIII for hemophilia A and FIX for hemophilia B), long-acting CFCs (i.e., extended half-life (EHLs)), non-factor, and gene therapies. The frequency of injections varies but overall injection burden is high. The WFH split treatment recommendations for hemophilia A with inhibitors (HAwI) and hemophilia B with inhibitors (HBwI) based on whether the inhibitor is low-responding or high-responding. The WFH recommends FVIII concentrate for hemophilia A patients with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate) for those with high-responding inhibitors. Hemophilia B patients with low-responding FIX inhibitors, use of a FIX-containing product to treat acute bleeds is recommended. Whereas for those with high-responding FIX inhibitors, rFVIIa is preferred. Additionally, HAwI and HBwI patients may undergo immune tolerance induction (ITI) to eradicate the inhibitor and, thus, allow the patient to return to ordinary CFC replacement therapies. The basic approach used by ITI is to give large doses of FVIII for FIX, often daily, for months or years. The relative success rate of ITI can be low and is only guideline recommended for HAwI though it can be used in HBwI. For patients with hemophilia A who develop persistent

low responding inhibitors, the WFH suggests that immune tolerance induction ITI be considered. Guidelines have not been updated to include fitusiran (Qfitlia).

VI. There are varying severities of hemophilia A and B depending on the level of factor produced by the patient, these are divided into the following per the International Society on Thrombosis and Hemostasis (ISTH):
    - Severe: <1% factor activity (<0.01 IU/mL)
    - Moderate: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
    - Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)

VII. There is a lack of strong scientific evidence from randomized controlled trials supporting the efficacy and safety of multiple agents for routine prophylaxis used in combination. Therefore, use of fitusiran (Qfitlia) in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.] is not allowable per policy. There is a lack of head-to-head trials showing superior safety or efficacy comparing fitusiran (Qfitlia) to other prophylactic agents for the treatment of hemophilia A or B. Given the known safety, established efficacy, and cost-effectiveness of these therapies, prior prophylaxis with emicizumab-kxwh (Hemlibra) remains the preferred specialty agents by this plan due to efficacy, safety, and cost. Fitusiran (Qfitlia) is specifically more costly than other agents, despite not having any evidence of improved clinical efficacy or safety.

VIII. Fitusiran (Qfitlia) was studied in three Phase 3 trials under the ATLAS clinical trial program (ATLAS-INH, ATLAS-A/B, and ATLAS-PPX) with a dose of 80mg administered monthly. After the completion of these parent studies, patients were rolled over into the long-term extension study (ATLAS-OLE) whose revised AT-based dosing regimen (AT-DR) (50mg Q2M) is to inform the labeled indication. ATLAS-OLE consisted of 227 PwHA/B with and without inhibitors. Participants averaged 30.7 years of age (range 13-72), hemophilia A (76.7%), hemophilia B (23.3%) and 12% were from North America. The primary efficacy outcome was long-term safety and efficacy as measured by an estimated mean ABR. An integrated analysis was completed to compare the fitusiran (Qfitlia) revised AT-DR as compared to comparative therapy arms in the parent trials.

IX. Results of ATLAS-OLE showed fitusiran (Qfitlia) was able to significantly reduce the estimated ABR as compared to bypassing agents (BPA) on-demand, CFC on-demand, and BPA prophylaxis therapies. When compared to CFC prophylaxis however, fitusiran (Qfitlia) was non-inferior to CFC prophylaxis (p=0.61). The observed median ABR (IQR) among all patients within the ATLAS-OLE primary efficacy period was 3.7 (0.0 to 7.5), 1.9 (0.0 to 5.6) in patients with inhibitors, and 3.8 (0.0 to 11.2) in patients without inhibitors. Lastly, 31.5% of patients were able to achieve zero bleeds while 47.2% were able to achieve one bleed event or less on prophylaxis therapy with fitusiran (Qfitlia). A total of 78% participants were maintained on Q2M regimens, of which 38% required zero dose adjustments and 56% required one dose adjustment to achieve AT 15–35%.

X. Secondary endpoints, including those measuring patient reported outcomes, were not assessed as a part of the ATLAS-OLE trial. Data from the parent trials demonstrated reductions in the Haem-A-QoL transformed total and physical scores though results meeting minimal clinically important differences were mixed. There are remaining limitations and unknowns specifically in regard to the small sample size of the trial, open-label trial design, lack of long term safety data with the AT-DR, lack of statistically significant QoL measures in certain treatment populations (Fitusiran versus prophylaxis (BPA/CFC) for the treatment of hemophilia A or B) and lack of comparative efficacy data to other hemophilia products of special interest (Hemlibra). Given the

combination of data and reduction in mean ABR across trial populations the level of evidence is considered moderate.

XI. Fitusiran (Qfitlia) was not directly compared with prophylaxis with emicizumab-kxwh (Hemlibra) therapy for the treatment of hemophilia A. Balancing long-term safety data, efficacy, and costs of alternative therapies compared to fitusiran (Qfitlia), treatment with emicizumab-kxwh (Hemlibra), when applicable, is required.

XII. When antithrombin levels are reduced, the clotting cascade can continue to function leading to hemostasis. It is hypothesized that an antithrombin level of less than 25% may lead to a desirable reduction in annualized bleed rate. The mechanism of fitusiran (Qfitlia) blocks the production of antithrombin to rebalance hemostasis. In clinical trials vascular thrombotic events did occur in five individuals. Individuals with thrombotic events had lower levels of AT (<10%). Therefore, under amended protocol for ATDR it's recommended to discontinue fitusiran (Qfitlia) if AT is measured at <15% on two repeated measurements.

XIII. Per the FDA label, AT activity is to be measured using an FDA-cleared test at Weeks 4 (Month 1), 12 (Month 3), 20 (Month 5), and 24 (Month 6) following the starting dose and after any dose modification. If any AT activity is 35% after 6 months, or if the patient has not achieved satisfactory bleed control, dose escalation should be considered. AT measurements should be restarted after a dose escalation.

Investigational or Not Medically Necessary Uses

I. Fitusiran (Qfitlia) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fitusiran (Qfitlia) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
   B. Pediatric patients <12 years of age with hemophilia A or B
   C. Von Willebrand disease

Appendix

Dose Modification Based on Antithrombin Activity Levels

Last Dosage Administered	Antithrombin Activity Level	Dose Modification	Quantity Limit
50mg every 2 months	Less than 15%	20mg every 2 months	0.2mL/56 days
	15% to 35%	Continue current dosage	0.5mL/56 days
	Greater than 35% after 6 months	50mg every month	0.5mL/28 days
20mg every 2 months	Less than 15%	10mg every 2 months	0.2mL/56 days
	15% to 35%	Continue current dosage	0.2mL/56 days
	Greater than 35% after 6 months	20mg every month	0.2mL/28 days
10mg every 2 months	Less than 15%	Discontinue fitusiran (Qfitlia)	N/A
	15% to 35%	Continue current dosage	0.2mL/56 days
	Greater than 35% after 6 months	10mg every month	0.2mL/28 days

References

1. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. Hemophilia. 2020: 26(Suppl 6): 1-158.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

2. Young G, Srivastava A, Kavakli K, Ross C, Sathar J, You CW, Tran H, Sun J, Wu R, Poloskey S, Qiu Z, Kichou S, Andersson S, Mei B, Rangarajan S. Efficacy and safety of fitusiran prophylaxis in people with hemophilia A or hemophilia B with inhibitors (ATLAS-INH): a multicentre, open-label, randomised phase 3 trial. Lancet. 2023 Apr 29;401(10386):1427-1437.
3. Kenet G, Nolan B, Zulfikar B, Antmen B, Kampmann P, Matsushita T, You CW, Vilchevska K, Bagot CN, Sharif A, Peyvandi F, Young G, Negrier C, Chi J, Kittner B, Sussebach C, Shammas F, Mei B, Andersson S, Kavakli K. Fitusiran prophylaxis in people with hemophilia A or B who switched from prior BPA/CFC prophylaxis: the ATLAS-PPX trial. Blood. 2024 May 30;143(22):2256-2269.
4. Srivastava A, Rangarajan S, Kavakli K, Klamroth R, Kenet G, Khoo L, You CW, Xu W, Malan N, Frenzel L, Bagot CN, Stasyshyn O, Chang CY, Poloskey S, Qiu Z, Andersson S, Mei B, Pipe SW. Fitusiran prophylaxis in people with severe hemophilia A or hemophilia B without inhibitors (ATLAS-A/B): a multicentre, open-label, randomised, phase 3 trial. Lancet Haematol. 2023 May;10(5):e322-e332.
5. Fitusiran unapproved product dossier. Sanofi. March 18, 2024.

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
emicizumab-kxwh (Hemlibra®) – Hemophilia A	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors
Standard Half-life Factor VIII Products – Hemophilia A	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management
Standard Half-life Factor IX Products – Hemophilia B	Control and prevention of bleeding episodes
	Perioperative management
	Routine Prophylaxis
Bypassing Agents – Hemophilia A & B	Control and prevention of bleeding – Hemophilia A or B with inhibitors
	Routine prophylaxis – Hemophilia A or B with inhibitors
	Perioperative management – Hemophilia A or B with inhibitors
	Control and prevention of bleeding episodes – Acquired hemophilia
	Control and prevention of bleeding episodes – Factor VII deficiency
	Control and prevention of bleeding episodes – Glanzmann's Thrombasthenia
	Perioperative management – acquired hemophilia
	Perioperative management – factor VII deficiency
	Perioperative management – Glanzmann's Thrombasthenia
Extended Half-life Factor VIII Products – Hemophilia A	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management
Extended Half-life Factor IX Products – Hemophilia B	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management
marstacimab (Hympavzi™)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with Hemophilia A or Hemophilia B without factor inhibitors
Concizumab (Alhemo®)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with Hemophilia A or Hemophilia B with factor inhibitors

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2025

Policy Type: PA/SP Pharmacy Coverage Policy: UMP314

Description

Foscarbidopa/foslevodopa (Vyalev) is a prodrug combination of foscarbidopa (carbidopa-4´-monophosphate) and foslevodopa (levodopa-4´-monophosphate), which are converted *in vivo* to carbidopa and levodopa.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
Foscarbidopa/foslevodopa (Vyalev)	Treatment of motor fluctuations in adults with advanced Parkinson's disease	120 mg foscarbidopa and 1,200 mg foslevodopa per 10 mL subcutaneous solution	42 vials/28 days*

**Quantity limits may be required if requesting over 42 vials/28 days. May request up to the maximum dose per label*

Initial Evaluation

I. **Foscarbidopa/foslevodopa (Vyalev)** 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 **Parkinson's Disease (PD)** when the following are met:
      1. Documentation that the member has advanced Parkinson's disease symptoms; **AND**
      2. Member is experiencing "off" episodes such as muscle stiffness, slow movements, or difficulty starting movements; **AND**
      3. Member's disease is responsive to treatment with levodopa with clearly defined "on" periods; **AND**
      4. The member is currently being treated with at least 400mg of levodopa per day; **AND**
   D. Provider attests to at least one of the following:
      1. Member is experiencing severe, troublesome motor fluctuations despite optimal oral or transdermal levodopa or adjunctive therapies; **OR**
      2. Member is experiencing inconsistent response to levodopa treatment; **OR**
      3. Member experiences dyskinesia or motor fluctuations that require frequent treatment adjustment without apparent benefit; **OR**
      4. Provider attestation motor fluctuations are causing disability or reduced quality of life; **AND**
   E. Member has experienced therapeutic failure or intolerance to one of the following oral carbidopa/levodopa products:

1. Carbidopa/levodopa IR dosed at least four times daily; **OR**
2. Carbidopa/levodopa XR/CR/ER; **AND**

F. Treatment with at least one agent in each of the following classes, used as an adjunctive treatment to levodopa/carbidopa has been ineffective, not tolerated, or all are contraindicated:
   1. Dopamine agonist (e.g., pramipexole, ropinirole, rotigotine)*; **OR**
   2. Monoamine oxide –B (MAO-B) inhibitor (e.g., rasagiline, safinamide, selegiline)*; **OR**
   3. Catechol-O-methyl transferase (COMT) inhibitor (e.g., entacapone, opicapone, tolcapone)*

*Please note: medications notated with an asterisk may require additional review

II. Foscarbidopa/foslevodopa (Vyalev) is considered investigational when used for all other conditions, including but not limited to:
   A. Mild Parkinson's disease symptoms
   B. Parkinson's disease WITHOUT documentation of motor fluctuations, "wearing off" phenomenon

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., experienced improvement in motor symptoms, reduction in 'off' periods, etc.]

Supporting Evidence

I. 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.
II. Motor symptoms in PD affect as many as 77% of patients; these include physical, visible signs of PD: resting tremor, muscular rigidity, postural instability. These advance into falls, axial postural deformities, dysphagia, and in advanced disease, these pharyngeal dysfunctions have an increase aspiration risk and lead to higher numbers of upper respiratory tract infections and pneumonia. Pharmacotherapies for managing the symptoms of PD show the greatest efficacy early in the course of the disease. As symptoms become refractory to standard therapies, levodopa, patients begin experiencing fluctuations in symptoms (OFF periods) within two years of beginning therapy.
III. Levodopa, administered in oral carbidopa/levodopa formulations, is the mainstay and most effective medication for management of PD motor symptom management. Currently, motor fluctuations are managed by increasing the patient's levodopa dose, reducing intake of dietary protein with levodopa administration, using longer acting carbidopa/levodopa formulations, and adding other agents that can be clinically useful in extending "on" time

(e.g., dopamine agonists, a catechol-O-methyl transferase (COMT) inhibitor, and/or a monoamine oxidase type B (MAO-B) inhibitor). A commonly encountered motor fluctuation is patients experiencing a “wearing off" near the end of the levodopa dose interval. For most patients who experience "wearing off" on a low dose of levodopa (e.g., ≤200 mg per dose), it is recommended to increase the levodopa dose. For patients who continue to experience "wearing off" at higher doses or who cannot tolerate higher doses due to dyskinesia, it is recommended to reduce the dose interval (with smaller individual doses of levodopa) and adding as needed extra doses at the end of the day. For patients with morning "wearing off" on immediate-release (IR) levodopa, adding on a bedtime dose of carbidopa-levodopa controlled-release (CR) tablet formulation may be beneficial; however, using CR tablets during the day may worsen motor fluctuations and lead to delayed-onset dyskinesia. Carbidopa-levodopa extended-release (ER) capsules show potential in reducing motor complications, but their broader use may be limited by cost and challenges in transitioning from levodopa tablets to ER capsules.

IV. Adding a dopamine agonist (e.g., pramipexole, ropinirole, or rotigotine), a COMT inhibitor (e.g., entacapone, opicapone, or tolcapone), or MAO-B inhibitors (rasagiline, safinamide, or selegiline) may be needed if adjustments to levodopa for "wearing off" are insufficient or poorly tolerated. These options have comparable effects and are cost effective standards of care. While the choice of medication should be personalized for each patient, the primary considerations when adding adjunctive medications are the potential for worsened dyskinesia and nonmotor dopaminergic side effects (e.g., impulse control disorders, orthostatic hypotension, hallucinations, sleep disturbances, etc.). Given the high cost of foscarbidopa/foslevodopa (Vyalev), trials of several “wearing off” treatment options are available and should be considered prior to coverage.

V. Device-assisted and surgical treatments are also available to improve motor function in selected patients with advanced PD and motor fluctuations, whose condition cannot be further improved by medical therapy. These treatments may include deep brain stimulation (DBS), focused ultrasound therapy (FUS), continuous levodopa-carbidopa intestinal gel (Duopa) infusion, and continuous subcutaneous apomorphine infusion (Apokyn, Kynmobi).

VI. Advanced Parkinson’s disease is not well defined in clinical literature, however advanced PD may be described as the later stages of the disease when symptoms have progressed significantly and impact daily life. Clinical trials often define advanced PD based on the presence of motor fluctuations, emergence of dyskinesia, and/or a certain amount of motor “off” time in a day and use progression of motor symptoms as a marker. Additional clinical features may include more difficulty with completing activities of daily living, severe motor fluctuations (tremors, rigidity, slow movement, increasing falls, motor “off” time in a day), non-motor symptoms (sleep disturbances, depression, anxiety), and emergence of cognitive decline (confusion, hallucinations, memory loss).

VII. A Phase 3, 12-week, randomized, double-blind, double-dummy, active-controlled study compared the efficacy, safety, and tolerability of foscarbidopa/foslevodopa (Vyalev) to oral carbidopa-levodopa in patients with advanced Parkinson’s Disease (PD). The study included patients ≥30 years of age with idiopathic PD that is levodopa-responsive. Participants must have been taking a minimum of 400 mg/day of Levodopa equivalents, have motor symptoms inadequately controlled by current therapy, have recognizable/identifiable "Off"

and "On" states (motor fluctuations), and have an average "Off" time of at least 2.5 hours/day over 3 consecutive PD Diary days with a minimum of 2 hours each day. Non-levodopa-containing concomitant PD medications (e.g., dopamine agonists, MAO-B inhibitors, and amantadine) were allowed but regimens had to remain unchanged until study completion. A total of 141 patients were randomized 1:1 receiving either 24-hour/day continuous subcutaneous infusion of foscarbidopa/foslevodopa (Vyalev) plus oral placebo capsules (N=74) or 24-hour/day continuous subcutaneous infusion of a placebo solution plus oral carbidopa-levodopa IR tablets (N=67). The primary endpoint of good "on" time (defined as "on" time without dyskinesia plus "on" time with non-troublesome dyskinesia), was collected and averaged over three consecutive days and normalized to a typical 16-hour waking period. Secondary endpoints evaluated changes from baseline in normalized “off” time. Compared with oral carbidopa-levodopa, foscarbidopa/foslevodopa (Vyalev) showed a significantly greater increase in “on” time without troublesome dyskinesia (mean 2.72 vs. 0.97 hours; difference 1.75 hours; 95% CI (0.46 to 3.05); P = 0.008) and a significantly greater reduction in “off” time (−2.75 vs. −0.96 hours; difference −1.79 hours; 95% CI (−3.03 to −0.54); P = 0.005). Improvements in "on" time were observed as early as the first week and persisted throughout the 12 weeks. Tolerability and safety with long-term foscarbidopa/foslevodopa (Vyalev) were maintained in the 96-week open label extension (OLE) trial. Foscarbidopa/foslevodopa (Vyalev) was generally safe and well tolerated. Adverse events (AEs) were reported in 85% of patients in the foscarbidopa/foslevodopa (Vyalev) group versus 63% in the carbidopa-levodopa group. The most frequent AEs in foscarbidopa/foslevodopa (Vyalev) treatment arm (≥10%) were infusion/catheter site reactions, infusion/catheter site infections, hallucinations, and dyskinesias, most of which were nonserious and mild to moderate in severity. The incidence of serious adverse events was generally similar between the treatment groups. Overall, the systemic safety profile of foscarbidopa/foslevodopa (Vyalev) was consistent with the established safety profile of other levodopa-containing therapies.

VIII. One-quarter of participants in the foscarbidopa/foslevodopa (Vyalev) group had their motor symptoms controlled exclusively foscarbidopa/foslevodopa (Vyalev) in the absence of scheduled concomitant PD medications. Further investigation is needed to fully assess the potential of foscarbidopa/foslevodopa (Vyalev) to reduce or eliminate the simultaneous use of concomitant Parkinson’s disease medications. Additionally, there were no significant changes in morning akinesia, sleep, or quality of life after adjusting for multiple analyses; However, numerical improvements indicate potential benefits of continuous 24-hour foscarbidopa/foslevodopa (Vyalev) continuous subcutaneous administration and merit further exploration.

IX. In order to be effective, device-assisted and surgical therapies (e.g., DBS, LCIG, CSAI) require the patient to still retain a response to levodopa, albeit can be compromised by motor complications or other side effects of therapy.

X. Foscarbidopa/foslevodopa (Vyalev) may offer a more convenient treatment option for the patient population that is currently addressed by Duopa and may replace oral levodopa-containing medications and catechol-O-methyltransferase (COMT) inhibitors for patients transitioning to it, but patients may be on other agents (e.g. MAO-B inhibitors, dopamine agonists) for the treatment of advanced PD. A reduction in concomitant PD medications,

followed by an adjustment in foslevodopa/foscarbidopa dosage, may be considered during therapy. Subthalamic nucleus deep brain stimulation (STN-DBS) is a surgical option for patients with advanced PD and motor complications refractory to oral treatment. Foscarbidopa/foslevodopa (Vyalev) may serve as a bridge for patients with advanced PD who are no longer adequately controlled with oral medications but whose PD is not advanced enough to warrant STN-DBS.

XI. As prodrugs of carbidopa-levodopa, foscarbidopa/foslevodopa (Vyalev) has higher solubility than both oral carbidopa-levodopa and carbidopa-levodopa enteral suspension (Duopa), which may allow for reduced volume and drug to be delivered subcutaneously. Both delivering continuous carbidopa-levodopa to patients with advanced PD, carbidopa-levodopa enteral suspension (Duopa) is an enteral suspension gel of carbidopa-levodopa that is delivered continuously by a pump through a PEG-J procedure tube into the small intestine as a continuous daytime (16-hour) infusion. Duopa requires surgery for placement of the tube into the small intestine/jejunum.

XII. The set quantity limit is less than maximum recommended dose and QLEs may be appropriate so long as max TDD per label is not exceeded (see appendix below).

Investigational or Not Medically Necessary Uses

I. Foscarbidopa/foslevodopa (Vyalev) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Mild Parkinson's disease symptoms
      i. Foscarbidopa/foslevodopa (Vyalev) has not been studied in patients with mild Parkinson's disease or Parkinson 's disease without motor fluctuations; therefore, it would be considered investigational when Foscarbidopa/foslevodopa (Vyalev) is requested in those settings.
   B. Parkinson's disease WITHOUT documentation of motor fluctuations, "wearing off" phenomenon

Appendix

I. Foscarbidopa/foslevodopa (Vyalev) is administered for subcutaneous administration only, preferably in the abdomen via the VYAFUSER pump. Patients must be trained on the proper use of foscarbidopa/foslevodopa (Vyalev) and the delivery system prior to initiating. The maximum recommended daily dosage of foscarbidopa/foslevodopa (Vyalev) is 3,525 mg of foslevodopa (approximately 2,500 mg levodopa). Available as cartons of 7 x 10-mL vials.
   a. Dosing and Instructions for use: vyalev_pat_vyafuserpump.pdf
   b. The dose may be adjusted to reach a clinical response that maximizes the functional "On" time and minimizes the number and duration of "Off" episodes and "On" episodes with troublesome dyskinesia.

XIII. Prescribing a backup oral carbidopa-levodopa product is recommended in the event that delivery of foscarbidopa/foslevodopa (Vyalev) is interrupted, which may result in underdosing. Patients should avoid sudden discontinuation or rapid dose reduction of foscarbidopa/foslevodopa (Vyalev), without administration of alternative dopaminergic therapy.

XIV. Foscarbidopa/foslevodopa (Vyalev) is contraindicated in patients who are currently taking a nonselective monoamine oxidase inhibitor (MAOi) or have recently (within 2 weeks) taken a nonselective MAOi. Nonselective MAOI's currently available in the United States include phenelzine (Nardil), isocarboxazid (Marplan), and tranylcypromine (Parnate). Hypertension can occur if these drugs are used concurrently.

References

1. Vyalev subcutaneous injection [prescribing information]. North Chicago, IL: AbbVie; October 2024.
2. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society
3. evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. Mov Disord. 2018;33(8):1248-1266
4. Soileau MJ, Aldred J, Budur K, et al. Safety and efficacy of continuous subcutaneous foslevodopa-foscarbidopa in patients with advanced Parkinson's disease: a randomised, double-blind, active-controlled, phase 3 trial [published correction appears in Lancet Neurol. 2023 Mar;22(3):e5. doi: 10.1016/S1474-4422(23)00048-0]. *Lancet Neurol*. 2022;21(12):1099-1109. doi:10.1016/S1474-4422(22)00400-8
5. Correction to Lancet Neurol 2022; 21: 1099-109. *Lancet Neurol*. 2023;22(3):e5. doi:10.1016/S1474-4422(23)00048-0
6. Aldred, J., et al. Continuous Subcutaneous Foslevodopa/Foscarbidopa in Parkinson's Disease: Safety and Efficacy Results From a 12-Month, Single-Arm, Open-Label, Phase 3 Study. *Neurol Ther.* 2023 Dec;12(6):1937-1958.
7. Freitas, ME., et al. Motor Complications of Dopaminergic Medications in Parkinson's Disease. Semin Neurol. 2017;37(2):147-157.
8. Aslam S, Manfredsson F, Stokes A, Shill H. "Advanced" Parkinson's disease: A review. *Parkinsonism Relat Disord*. 2024;123:106065. doi:10.1016/j.parkreldis.2024.106065
9. Liang, TW. Medical management of motor fluctuations and dyskinesia in Parkinson disease. In Post T, ed. UpToDate. UpToDate; 2024. Accessed January 10, 2025. www.uptodate.com

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
pimavanserin (Nuplazid) Policy	Parkinson's disease psychosis
istradefylline (Nourianz) Policy	Parkinson's disease
levodopa (Inbrija) Policy	Parkinson's disease
apomorphine (Apokyn, Kynmobi) Policy	Parkinson's disease

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	01/2025

fruquintinib (Fruzaqla™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP290

Description

Fruquintinib (Fruzaqla) is a selective vascular endothelial growth factor (VEGF) receptor kinase inhibitor.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
fruquintinib (Fruzaqla)	Metastatic colorectal cancer (mCRC)	1 mg cap	84 caps/28 days
		5 mg cap	21 caps/28 days

Initial Evaluation

I. **Fruquintinib (Fruzaqla)** 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. Medication is not used in combination with any other oncology therapy; **AND**
   D. A diagnosis of **metastatic colorectal cancer (mCRC)**; **AND**
      1. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, etc.), oxaliplatin, and irinotecan-based chemotherapy; **AND**
      2. The member has been previously treated with an anti-VEGF therapy (e.g. bevacizumab, Zaltrap, Cyramza, etc.); **AND**
      3. Treatment with trifluridine-tipiracil (Lonsurf) has been ineffective, contraindicated, or not tolerated; **AND**
      4. The tumor has been tested and is documented to be RAS mutant-type; **OR**
         i. The tumor has been tested and is documented to be RAS wild-type; **AND**
            a. The tumor is a right-sided tumor; **OR**
            b. The tumor is a left-sided tumor; **AND**
               i. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab)

II. **Fruquintinib (Fruzaqla)** is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Fruquintinib (Fruzaqla) used in combination with another oncology therapy
   B. Gastroesophageal junction adenocarcinoma
   C. Breast cancer
   D. Non-small cell lung cancer (NSCLC)

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

E. Soft tissue sarcoma
F. Advanced pancreatic 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. Clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
IV. Medication is not used in combination with any other oncology therapy

Supporting Evidence

I. Colorectal cancer (CRC) is the third most prevalent cancer worldwide and the second most common cause of cancer death in the United States. Initial clinical presentation as mCRC occurs in approximately 20% of patients and nearly 70% of patients with localized disease eventually develop metastases. In 2023, approximately 150,000 individuals will be diagnosed with CRC and over 50,000 individuals will die from the disease. Given the complexity of management of mCRC, the treatment of mCRC must be initiated by, in or consultation with, an oncologist.
II. CRC originates from the epithelial tissue of the colon, and it may develop either on the right side or left side of the colon. Therapeutic responses, disease progression, and overall survival vary depending on the position of the tumor. The difference between left and right tumors can be attributed to anatomical and developmental origin, or distinct carcinogenic factors (such as difference in bacterial population) or a combination of both. Multiple retrospective analyses (CRYSTAL, FIRE-3, and Canadian NCIC CO.17 trial) found that left-sided CRC has a better prognosis and responds better to anti-EGFR therapy compared to right-sided CRC. Studies have demonstrated that anti-EGFR therapies improved the overall survival in patients with left-sided KRAS wild type tumors, but not in patients with right-sided wild type tumors.
    - Right-sided tumors occur in the ascending colon, and proximal two thirds of the transverse colon and mutations in the DNA mismatch repair pathway are commonly observed. These tumors generally have a flat histology and are harder to diagnose, which may result in more advanced and larger tumors at diagnosis. Right-sided CRC patients do not respond well to anti-EGFR therapy. Microsatellite DNA mismatch repair pathway (MSI or dMMR) may be an important prognostic factor to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease.
    - Left-sided tumors occur in the descending and sigmoid colon, and distal one third of the transverse colon and chromosomal instability pathway-related mutations, such as KRAS, APC, PIK3CA, p53 mutations, are more commonly observed. These tumors generally have polypoid-like morphology, which makes them easier to diagnose in early stages of carcinogenesis. Up to 85% of CRC are left-sided tumors. Left-sided CRC patients benefit more from targeted therapies such as anti- epidermal growth factor receptor (EGFR) therapy, due to the pathway-related mutation.

III. Fruquintinib (Fruzaqla) is the fifth FDA-approved anti-VEGF agent indicated for treatment of mCRC. Fruquintinib (Fruzaqla) is the first and only selective inhibitor of all three VEGF receptor kinases for previously treated mCRC regardless of biomarker status. It is FDA-approved for the treatment of metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. Fruquintinib (Fruzaqla) is an oral capsule given once daily for 21 days out of a 28-day cycle.

IV. The National Comprehensive Cancer Network (NCCN) guidelines recommend fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy with or without bevacizumab as first and second line therapy, with immune checkpoint inhibitors, anti-epidermal growth factor receptor (EGFR) agents if RAS wildtype, and anti-VEGF therapy. NCCN guidelines recommend fruquintinib (Fruzaqla) as a third line treatment (category 2A) for mCRC, joining trifluridine-tipiracil (Lonsurf) ± bevacizumab and regorafenib (Stivagra) as category 2A recommended agents. NCCN guidelines recommend anti-EGFR therapy prior to fruquintinib (Fruzaqla) in mCRC, RAS wild type, left-sided tumors.
    - NCCN guidelines remain silent on the best sequence of therapy in the third- and fourth-line setting. The FRESCO-2 trial permitted previous treatment with trifluridine-tipiracil (Lonsurf) prior to randomization, and 91% of participants received prior trifluridine-tipiracil (Lonsurf) therapy. As the majority of participants had prior trifluridine-tipiracil (Lonsurf) therapy, requiring step through trifluridine-tipiracil (Lonsurf) is both clinically appropriate and cost-effective.

V. Fruquintinib (Fruzaqla) was studied in a Phase 3, international, multicenter, randomized (2:1), double-blinded, placebo-controlled study (FRESCO-2) in 691 patients with mCRC who had received all current standard approved cytotoxic and targeted therapies [fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti- EGFR therapy (if RAS wild type)] and progressed on, or were intolerant to, trifluridine-tipiracil and/or regorafenib. Participants were randomized to receive fruquintinib (Fruzaqla) 5mg daily in addition to best supportive care (BSC) or placebo with BSC. Baseline characteristics were similar between both groups: median age 64 years, 63% of patients had RAS mutation, median number of previous therapies was four (96% of patients received previous anti-VEGF therapy and all participants received trifluridine-tipiracil (Lonsurf) and/or regorafenib (Stivara). The median OS was 7.4 months for the fruquintinib-treated group compared to 4.8 months for the placebo group, HR 0.66 (95% CI 0·55–0·80; p<0·0001).

VI. Fruquintinib (Fruzaqla) was also studied in a randomized, double-blinded, placebo-controlled, multicenter, Phase 3 clinical trial completed in China (FRESCO). A total of 416 participants aged 18-75 years with mCRC that progressed after 2 lines of chemotherapy were randomized in a 2:1 ratio to receive either fruquintinib (Fruzaqla) 5mg daily plus best supportive care or placebo with best supportive care. Median overall survival was significantly prolonged with fruquintinib (Fruzaqla) compared with placebo (9.3 months [95% CI, 8.2-10.5] vs 6.6 months [95% CI, 5.9-8.1]); HR 0.65 (95% CI, 0.51-0.83; P<0.001). However, at the time of the study, standard treatment practices for metastatic colorectal cancer in China were not the same as the standard treatment practices in the United States. Only one-third of the patients had received previous anti-VEGF therapy, and none had received trifluridine–tipiracil or regorafenib.

VII. The safety profile of fruquintinib (Fruzaqla) is similar to that of other FDA-approved anti-VEGF agents indicated for mCRC. Adverse events did occur more frequently in the fruquintinib (Fruzaqla) group compared to placebo. The most common adverse events were hypertension (37% vs 9%), asthenia (34% vs 23%), and hand-foot syndrome (19% vs 3%). A total of 93 (20%) patients who received fruquintinib (Fruzaqla) and 49 (21%) who received placebo discontinued

treatment due to adverse events (asthenia and gastrointestinal perforation, proteinuria, and elevated LFTs).

VIII. The use of fruquintinib (Fruzaqla) has not been studied in combination with other oncology therapies, and 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. Fruquintinib (Fruzaqla) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fruquintinib (Fruzaqla) used in combination with another oncology therapy. Fruquintinib (Fruzaqla) was studied as monotherapy in the FRESCO and FRESCO-2 trials.
   B. Gastroesophageal junction adenocarcinoma
      i. Fruquintinib plus paclitaxel demonstrated improvements in progression-free survival, objective response rate, disease control rate, and more, in patients with advanced gastric or gastroesophageal junction adenocarcinoma in a Phase 3 FRUTIGA study. Results are to be shared with the China National Medical Products Administration.
   C. Breast cancer
      i. There is an ongoing open-label study evaluating fruquintinib in HER2- breast cancer (NCT03251378)
   D. NSCLC
      i. There was a withdrawn trial evaluating fruquintinib in NSCLC
   E. Soft tissue sarcoma
      i. There is a recruiting trial evaluating fruquintinib in chemotherapy resistant soft tissue sarcoma in China (NCT05142631)
   F. Advanced pancreatic cancer – Phase 2 trial evaluating fruquintinib in advanced pancreatic cancer in China

References

1. Dasari A, Lonardi S, Garcia-Carbonero R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet. 2023;402(10395):41-53.
2. Li J, Qin S, Xu RH, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. JAMA. 2018;319(24):2486-2496.
3. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Versions 4.2023 – Nov 16, 2023). 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 1, 2023.
4. Fruzaqla (fruquintinib) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals; November 2023.
5. UpToDate, Inc. Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy. UpToDate [database online]. Waltham, MA. Last updated October 19, 2023. Available at: http://www.uptodate.com/home/index.html.

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 (Stivara®) Policy	Gastrointestinal stromal tumor, metastatic colorectal cancer, hepatocellular carcinoma
trifluridine/tipiracil (Lonsurf®) Policy	Stomach or esophagogastric adenocarcinoma, metastatic colorectal cancer
encorafenib (Braftovi®), binimetinib (Mektovi®) Policy	Malignant melanoma (BRAF V600E mutation), metastatic colorectal cancer with BRAF V600E mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed split fill requirement as package in unbreakable	08/2024
Policy created	02/2024

Policy Type: PA Pharmacy Coverage Policy: UMP197

Description

Gabapentin ER (Gralise) is an orally administered anticonvulsant. Gabapentin enacarbil (Horizant) is a prodrug of gabapentin.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
gabapentin ER (Gralise)	300 mg tablets	Postherpetic neuralgia	60 tablets/30 days
	450 mg tablets		
	600 mg tablets		
	750 mg tablets		
	900 mg tablets		
	300 mg-600mg tablets Blister/Starter Pack		33 tablets (1 pack)/30 days
generic gabapentin ER	300 mg capsules	Postherpetic neuralgia	60 capsules/30 days
	600 mg capsules		
gabapentin enacarbil (Horizant)	300 mg tablets	Postherpetic neuralgia; Restless leg syndrome	30 tablets/30 days
	600 mg tablets		60 tablets/30 days

Initial Evaluation

I. **Gabapentin ER (Gralise) or gabapentin enacarbil (Horizant)** 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 one of the following:
      1. **Postherpetic neuralgia (PHN); AND**
         i. Treatment with gabapentin, greater than or equal to, 1800 mg per day has been ineffective, contraindicated, or not tolerated; **AND**
         ii. Treatment with pregabalin has been ineffective, contraindicated, or not tolerated; **AND**
         iii. If the request is for brand gabapentin ER (Gralise) 300mg or 600mg, treatment with generic gabapentin ER 300mg or 600mg has been ineffective, not tolerated, or contraindicated; **OR**
            a. Request is for 450mg, 750mg, 900mg, or 300mg-600mg starter pack; **OR**

2. **Moderate-to-severe primary restless leg syndrome**; **AND**
    i. Request is for gabapentin enacarbil (Horizant); **AND**
    ii. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated:
        a. pramipexole; **AND**
        b. ropinirole; **AND**
        c. pregabalin

II. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) are considered investigational when used for all other conditions, including but not limited to:
    A. Diabetic peripheral neuropathy
    B. Postmastectomy pain syndrome
    C. Seizures
    D. Other neuropathic pain

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. A diagnosis of one of the following:
    A. Restless Leg Syndrome (RLS); **AND**
        1. Member has exhibited improvement or stability of restless leg syndrome symptoms [e.g., improved pain, sleep, fatigue]; **OR**
    B. Postherpetic neuralgia (PHN); **AND**
        1. Member has exhibited improvement or stability of symptoms [e.g. improved pain, skin sensitivity].

Supporting Evidence

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for safety and efficacy in pediatric patients under the age of 18 years.
II. A phase 3, placebo-controlled, randomized trial has shown gabapentin ER (Gralise) to be efficacious in decreasing pain associated with postherpetic neuralgia over placebo (p=0.013). Phase 4 studies have similarly suggested effectiveness in pain reduction in patients with postherpetic neuralgia.
III. A phase 3, placebo-controlled, randomized trial has shown gabapentin enacarbil (Horizant) to be efficacious in reducing pain associated with postherpetic neuralgia over placebo (p=0.013) after 13 weeks.
IV. Guidelines for postherpetic neuralgia recommend immediate release gabapentin as a first line treatment option. It is recommended patients trial gabapentin IR before switching to an extended-release gabapentin product such as gabapentin ER (Gralise) or gabapentin enacarbil (Horizant).

V. Standard of care for treatment of postherpetic neuralgia includes use of pregabalin as first line therapy.

VI. A phase 4, placebo-controlled randomized trial found gabapentin enacarbil (Horizant) to improve restless leg syndrome symptoms on patient reported scales (IRLS) over placebo (p=0.014) as well as clinician-assessed (CGI-I) scales (p=0.004) after 12 weeks of treatment.

VII. Restless leg syndrome guidelines, as published by the American Academy of Neurology (AAN), recommend dopamine agonists (e.g. pramipexole, ropinirole, rotigotine) and gabapentin enacarbil (Horizant) as first line treatment options. A small (n=39) double-blind, placebo-controlled trial investigated a possible reduced response to gabapentin enacarbil (Horizant) following long-term dopaminergic treatment. A significant difference (p=0.045) in restless leg syndrome symptoms (IRLS) was found between dopamine treatment-naïve and dopamine treatment-experienced individuals when treated with gabapentin enacarbil (Horizant). Patients who were dopamine-experienced had been treated with a dopamine agonist for at least 90% of the past 5 consecutive years. Although gabapentin enacarbil (Horizant) is recommend as a first-line therapy along with dopamine agonists, due to the small sample size, as well as the unknown effects of shorter-term uses of dopamine agonists on gabapentin enacarbil (Horizant) responses, enacarbil (Horizant) should not be chosen as a first-line agent over a dopamine agonist.

VIII. Restless leg syndrome guidelines as published by the American Academy of Neurology (AAN) also lists pregabalin as having moderate evidence for use in treatment of RLS aligned with ropinirole, a dopamine agonist.

Investigational or Not Medically Necessary Uses

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   - A. Diabetic peripheral neuropathy
     - i. A placebo-controlled, randomized trial found no significant difference in efficacy from placebo and three different doses of gabapentin enacarbil (Horizant) in subjects with diabetic peripheral neuropathy.
   - B. Postmastectomy pain syndrome
     - i. A small (n=21) open-label study found a small positive improvement in pain intensity after 8 weeks with gabapentin ER (Gralise). Further placebo-controlled, randomized trials are needed to validate efficacy and safety for this indication.
   - C. Seizures
     - i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of seizures.
   - D. Other neuropathic pain
     - i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of neuropathic pain not associated with postherpetic neuralgia or restless leg syndrome.

References

1. Gralise [Prescribing Information]. Menlo Park, CA: Depomed. September 2012.
2. Horizant [Prescribing Information]. Research Triangle Park, NC: GSK. March 2013.

3. Gabapentin Enacarbil Adult Restless Leg Syndrome Post Marketing Commitment Study (CONCORD). *Clinicaltrials.gov.* 2014. (NCT 01668667)
4. Garcia-Borreguero D, et al. Reduced response to gabapentin enacarbil in restless legs syndrome following long-term dopaminergic treatment. Sleep Med. 2019 Mar;55:74-80. doi: 10.1016/j.sleep.2018.11.025.
5. Study of Safety and Effectiveness of GRALISE (Gabapentin) Tablets in the Treatment of Patients With Postherpetic Neuralgia in Clinical Practice. *Clinicaltrials.gov.* 2012 (NCT 01426230)
6. Belfer I, et al. Effect of gastroretentive gabapentin (Gralise) on postmastectomy pain syndrome: a proof-of-principle open-label study. Pain Rep. 2017 Apr 11;2(3):e596. doi: 10.1097/PR9.0000000000000596.
7. Rauck R, et al. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. Pain Pract. 2013 Jul;13(6):485-96. doi: 10.1111/papr.12014.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new 300mg and 600mg gabapentin ER to the QL table; Added step through generic gabapentin ER before use of Gralise when using the 300mg or 600mg tablets/capsules	01/2024
Added new 450mg, 750mg, 900mg once-daily tab Gralise strengths to the QL table	05/2023
Update to new policy format, addition of pregabalin as required agent to try and fail, removal of renal status related criteria	10/2020
Previous review	11/2011

ganaxolone (Ztalmy®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP260

Description

Ganaxolone (Ztalmy) is an orally administered neuroactive steroid gamma-aminobutyric acid A ($GABA_A$) receptor positive modulator.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
ganaxolone (Ztalmy)	Seizures associated with CDKL5 Deficiency Disorder (CDD)	50 mg/mL oral suspension	≤ 28 kg: Monthly quantity (in mL) to allow for a maximum of 63 mg/kg per day
			> 28 kg: Monthly quantity (in mL) to allow for a maximum of 1800 mg (36 mL) per day

Initial Evaluation

I. **Ganaxolone (Ztalmy)** may be considered medically necessary when the following criteria are met:
   A. Member is two years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of the member's weight, measured in the past three months (necessary for dose calculation); **AND**
   D. Will be used in combination with one or more antiseizure medications (e.g., clobazam [Onfi], valproate [Depakote], levetiracetam [Keppra], etc.); **AND**
   E. A diagnosis of **cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)** as evidenced by all of the following:
      1. Documentation of pathogenic or likely pathogenic CDKL5 mutation; **AND**
      2. Provider attestation that seizure onset occurred by one year of age; **AND**
      3. Provider attestation that member has motor and cognitive delays; **AND**
      4. Documentation of baseline seizure frequency and severity**; AND**
      5. Seizures are refractory to three or more antiseizure medications (e.g., clobazam [Onfi], valproate [Depakote], lamotrigine [Lamictal], levetiracetam [Keppra], rufinamide [Banzel], topiramate [Topamax], felbamate [Felbatol], stiripentol [Diacomit], zonisamide [Zonergan], vigabatrin [Sabril]).

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

II. Ganaxolone (Ztalmy) is considered investigational when used for all other conditions, including but not limited to:
   A. Infantile Spasms or West Syndrome
   B. Rett Syndrome
   C. Lennox-Gastaut Syndrome, Dravet Syndrome, Tuberous Sclerosis Complex
   D. Other non-FDA approved seizure disorders

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 the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
IV. Ganaxolone (Ztalmy) will continue to be used in combination with one or more antiseizure medications; **AND**
V. Member has exhibited improvement or stability of seizure frequency or severity.

Supporting Evidence

I. Length of authorization for initial approval is six months as clinical benefits of ganaxolone (Ztalmy) were evaluated at 17 weeks in the pivotal trial. Six months is sufficient for assessment of treatment response and to initiate medication renewal request.
II. Ganaxolone (Ztalmy) is FDA-approved for use in patients two years of age and older. Safety and efficacy of ganaxolone (Ztalmy) in younger patients has not been evaluated. Other antiseizure medications have been evaluated for safety and efficacy in as early as infancy.
III. Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare genetic disorder caused by a mutation in the CDKL5 gene, which is responsible for normal brain development and function, that results in severe developmental delay, intellectual disability, and seizures. CDD presents as early as three months after birth, primarily in the form of frequent, refractory spasms and seizures of various types. Additionally, motor and cognitive dysfunction become more prevalent over time, including behavioral dysregulation, movement disorders, hypotonia, visual impairment, sleep abnormalities, and gastrointestinal problems. CDKL5 gene mutations have also been identified in patients with infantile spasms, Rett, West and Lennox Gastaut Syndrome, autism and intractable epilepsy. However, CDD is a distinct disease characterized by symptoms of motor/cognitive delays and epilepsy with various seizure types within the first year of life. Given significant overlap with other types of developmental encephalopathies, treatment-resistant epilepsy, and movement disorders, diagnosis of CDD is made through presence of a pathogenic or likely pathogenic variant in the CDKL5 gene, presence of motor/cognitive delays, and onset of epilepsy within the first year of life.

IV. Given the specialized, high-touch care and monitoring required for CDD patients, ganaxolone (Ztalmy) must be prescribed by, or in consultation with, a neurologist.

V. There are no formal guidelines for management of CDD. Additionally, there are no currently available disease-modifying therapies for CDD, therefore treatment is supportive. Common treatment strategies for CDD-associated seizures include ketogenic diet, vagus nerve stimulator (VNS) placement, pharmacologic therapy with antiseizure medications, ACTH, or steroids, and neurosurgery. Experts recommend first-line therapy with a broad-spectrum antiseizure medication (e.g., valproate, levetiracetam, clobazam, zonisamide), and proceed with second trial or combination therapy as appropriate; VNS and neurosurgery are reserved for drug-resistant seizure. Seizure in CDD is known to be medically refractory, therefore it is common for CDD patients to have tried and continue to take multiple antiseizure medications concurrently. While ganaxolone (Ztalmy) is the only FDA-approved therapy for treatment of CDD-associated seizures, patients in the clinical program were required to be refractory to two or more antiseizure medications, the majority did not achieve clinically meaningful seizure reduction, and comparative efficacy to other antiseizure medications is unknown. Therefore, given the known extent of efficacy, established safety profile, and cost effectiveness of other antiseizure medications, at least three adequate efficacy trials are required prior to ganaxolone. Considering an abundance of available antiseizure medications, intolerance and early discontinuation do not meet definition of adequate efficacy trial.

VI. Ganaxolone (Ztalmy) was studied in one 17-week international, randomized, double-blind, placebo-controlled Phase 3 study: MARIGOLD. A total of 101 patients aged 2-21 years with molecularly confirmed CDD and a history of early-onset seizures uncontrolled by two or more antiseizure medications were enrolled. Use of up to four concomitant antiseizure medications during the study was allowed if stable on dose for at least one month, while patients being treated with glucocorticoids or ACTH were excluded. Population characteristics were as follows: 79% female, median age six years, median seven previous antiseizure medication trials, median two concomitant antiseizure medications including valproic acid, levetiracetam, clobazam and vigabatrin. The primary endpoint was percent change in median 28-day major motor seizure frequency (MMSF), with a 30.7% reduction in the ganaxolone group compared to a 6.9% reduction in the placebo group (P=0.0036). Secondary endpoints included proportion of patients with ≥ 50% reduction in 28-day MMSF, otherwise known as clinically meaningful reduction in seizure frequency, and quality of life as assessed through the Clinical Global Impression of Improvement (CGI-I) score by clinician and caregiver, none of which were met. Most common adverse events were somnolence, pyrexia, and upper respiratory tract infection; ganaxolone (Ztalmy) is a controlled substance due to abuse and dependence potential and has a warning for somnolence/sedation. Overall, the benefit of ganaxolone (Ztalmy) is modest and potential confounding background therapy limits application and usefulness in the intended population.

VII. During clinical trials, participants received ganaxolone (Ztalmy) as an adjunct to antiseizure therapy, with the majority taking a median of two concomitant antiseizure medications. Background seizure medications included, but were not limited to, valproate, levetiracetam, clobazam, vigabatrin, clonazepam, topiramate, zonisamide, rufinamide, lamotrigine, oxcarbazepine, etc. Only one patient in the ganaxolone group was taking ganaxolone as monotherapy. As such, efficacy and safety of ganaxolone as monotherapy remain unknown.

Investigational or Not Medically Necessary Uses

I. Ganaxolone (Ztalmy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Infantile Spasms or West Syndrome
   B. Rett Syndrome
   C. Lennox-Gastaut Syndrome, Dravet Syndrome, Tuberous Sclerosis Complex
   D. Other non-FDA approved seizure disorders

References

1. Ztalmy [Prescribing Information]. Marinus Pharmaceuticals, Inc: Radnor, PA. March 2022.
2. Knight EMP, Amin S, Bahi-Buisson N, et al. Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2022;21(5):417-427.
3. Olson HE, Demarest ST, Pestana-Knight EM, et al. Cyclin-dependent kinase-like 5 deficiency disorder: clinical review. Pediatr Neurol. 2019;97:18-25.
4. Olson HE, Daniels CI, Haviland I, et al. Current neurologic treatment and emerging therapies in CDKL5 deficiency disorder. J Neurodev Disord. 2021;13(1):40.
5. New drug review: Ztalmy (ganaxolone). IPD Analytics. April 2022. Accessed May 06, 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
cannabidiol (Epidiolex®) Policy	Lennox-Gastaut Syndrome
	Dravet Syndrome
	Tuberous Sclerosis Complex
vigabatrin (Sabril®, Vigadrone®) Policy	West Syndrome (Infantile Spasms)
	Refractory complex partial epileptic seizure, adjunct therapy
stiripentol (Diacomit®) Policy	Dravet Syndrome
fenfluramine (Fintepla®) Policy	Dravet Syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2022

gepirone ER (Exxua™)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP294

Description

Gepirone ER (Exxua) is an orally administered selective serotonin 1A (5HT1A) receptor agonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
gepirone ER (Exxua)	Major depressive disorder (MDD)	18.2 mg tablets	30 tablets/30 days
		36.3 mg tablets	
		54.5 mg tablets	
		72.6 mg tablets	

Initial Evaluation

I. **Gepirone ER (Exxua)** 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 **major depressive disorder (MDD)** when the following are met:
      1. Treatment with at least two medications in each of the following drug classes has been ineffective, contraindicated, or not tolerated:
         i. Selective serotonin reuptake inhibitors [SSRIs] (e.g., citalopram, fluoxetine, paroxetine, sertraline)
         ii. Serotonin-norepinephrine reuptake inhibitors [SNRIs] (e.g., desvenlafaxine succinate, duloxetine, venlafaxine)
         iii. Atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone); **AND**
      2. Treatment with vortioxetine (Trintellix)* has been ineffective, contraindicated, or not tolerated. (Please note: medications notated with an asterisk may require step therapy or non-formulary requirements prior to approval)

II. Geprione ER (Exxua) is considered investigational when used for all other conditions, including but not limited to:
   A. Generalized anxiety disorder (GAD)
   B. Substance use disorder
   C. Other psychiatric conditions

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ArrayRx administered by moda HEALTH

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., reduced HAMD-17 score, reduced suicidal thoughts/ideation, no ED or inpatient admissions]

Supporting Evidence

I. The FDA-approval of gepirone ER (Exxua) was based on two randomized, double-blind, placebo-controlled trials in a total of 457 adult patients with moderate to severe MDD. The primary efficacy outcome was change from baseline (CFB) in Hamilton Depression Rating Scale (HAMD-17) total score at week 8. Key secondary endpoints included CFB in Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impression-Severity (CGI-S) scale. All primary and key secondary outcomes were met and considered statistically significant. However, the numerical difference of CFB in the HAMD-17 score between gepirone ER (Exxua) and placebo did not meet the threshold for a clinically meaningful benefit (difference of 4 to 6 points) in either pivotal trial.

	Study 1 [134001]		Study 2 [FKGBE007]	
	Gepirone ER (N=101)	Placebo (N=103)	Gepirone ER (N=116)	Placebo (N=122)
CFB in HAMD-17 score	-9.77	-7.43	-10.2	-8.0
p-value	*P = 0.18*		*P=0.032*	
CFB MADRS	-12.28	-9.22	-13.7	-9.9
p-value	*P = 0.024*		*P=0.008*	
CFB CGI-S	-1.28	-0.88	-1.3	-0.09
p-value	*P = 0.016*		*P=0.015*	

II. Gepirone ER (Exxua) has been studied across numerous clinical trials over the past 30 years, with multiple attempts at gaining FDA approval dating back to the 1990s, and three failed attempts to secure approval prior to the successful submission in 2023.
III. Looking at the totality of evidence, there were 12 short-term trials conducted in the 1990s and early 2000s that have previously been included in FDA submission for approval; only two trials are considered positive, three uninformative, and seven negative. The four active-controlled trials did not detect a statistically significant change compared to placebo or active control for either the pre-specified endpoint or the ad-hoc primary analysis for HAMD-17 conducted by the FDA for comparison purposes. Interestingly, a statistically significant difference was detected in favor of the active control compared to gepirone ER (Exxua) in the ad-hoc analysis. Regardless of the active control result in the ad-hoc analysis, gepirone ER (Exxua) failed to meet the primary endpoint in both analyses compared to placebo and active control. Therefore, these trials are considered failed and negatively impact the quality of evidence. Therefore, the quality of evidence is considered low as there are multiple well-designed trials with mixed results in the efficacy of gepirone ER (Exxua).

IV. Although the results of the two pivotal trials showed a statistically significant change from baseline in HAMD-17 scores, this did not correlate to a clinically meaningful change compared to placebo. Due to a lack of clinically meaningful impact on depressive symptoms compared to placebo, in addition to multiple failed clinical trials with an active control, the value of gepirone ER (Exxua) as compared to standard of care antidepressant therapy remains unknown at this time and will be realized in real-world settings.

V. The majority of adverse events reported during the clinical program were considered mild or moderate in severity. The most reported adverse events during clinical trials for gepirone ER (Exxua) versus placebo, respectively, included dizziness (49% vs. 10%), nausea (35% vs. 13%), headache (31% vs. 20%), sleepiness (15% vs. 14%), and insomnia (14% vs. 5%). Gepirone ER (Exxua) carries labeled contraindications for prolonged QTc interval or long QT syndrome, hepatic impairment, and combination use with MAOIs and strong CYP3A4 inhibitors. Gepirone ER (Exxua) also carries a black box warning for increased risk of suicidal thoughts and behaviors, especially in the pediatric and young adult populations.

VI. Notably, sexual side effects were not widely reported during the clinical trial period. Therefore, gepirone ER (Exxua) may be seen as a favorable treatment option for patients who have experienced sexual side effects with a previous antidepressant. Although gepirone ER (Exxua) may have a lower incidence of sexual side effects associated with its use, bypassing treatment alternatives due to potential side effects is not considered a viable clinical rationale.

VII. For the treatment of MDD, American Psychiatric Association (APA) recommends either psychotherapy or a second-generation antidepressant (i.e., SSRI, SNRI, bupropion) for first-line therapy, switching to another antidepressant medication for second-line therapy, and augmentation with another antidepressant medication or adding psychotherapy for third-line therapy. Alternatively, augmentation with an antipsychotic may also be considered in the third line and subsequent therapy. Treatment effectiveness with generic antidepressants has been established by clinical trials and substantiated by real-world use. Therefore, the use of multiple generic antidepressants and lower cost branded antidepressants remains a reasonable approach to therapy and prioritizes use of high-value therapeutic options.

Investigational or Not Medically Necessary Uses

I. Gepirone ER (Exxua) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Generalized anxiety disorder (GAD)
   B. Substance use disorder
   C. Other psychiatric conditions

Appendix

I. Generic antidepressants by class

Selective Serotonin Reuptake Inhibitors (SSRIs)	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Atypical Antidepressants
Citalopram	Desvenlafaxine succinate	Bupropion (IR/SR/XL)
Escitalopram	Duloxetine	Mirtazapine
Fluoxetine	Venlafaxine (IR/ER)	Trazodone
Fluvoxamine (IR/ER)		Vilazodone

Paroxetine (IR/CR)		
Sertraline		

References

1. Exxua. Package Insert. Fabre-Kramer Pharmaceuticals; 2023.
2. Center for Drug Evaluation and Research. Application Number 021164Orig1s000 Multi-Discipline Review. Multidisciplinary Review and Evaluation: NDA 021164. Updated September 22, 2023. Available At: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/021164Orig1s000MultidisciplineR.pdf
3. Center for Drug Evaluation and Research. FDA Briefing Document – Psychopharmacologic Drugs Advisory Committee (PDAC) Meeting: NDA 021164. Updated December 1, 2015. Available At: https://www.fdanews.com/ext/resources/files/11-15/11-30-15-gepirone-FDA.pdf?1520792689
4. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from https://www.apa.org/depression-guideline
5. Feiger AD, Heiser JF, Shrivastava RK, et al. Gepirone Extended-Release: New Evidence for Efficacy in the Treatment of Major Depressive Disorder. J Clin Psychiatry. 2003; 64: 243-249.
6. Bielski RJ, Cunningham L, Horrigan JP, et al. Gepirone Extended-Release in the Treatment of Adult Outpatients with Major Depressive Disorder: A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study. J Clin Psychiatry. 2008; 69: 571-577.

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	02/2024

gilteritinib (XOSPATA®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP032

Split Fill Management*

Description

Gilteritinib (Xospata) is an orally administered FLT3 Tyrosine Kinase Inhibitor.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
gilteritinib (Xospata)	Relapse/Refractory FLT3-mutated Acute Myeloid Leukemia (AML)	40 mg tablets	90 tablets/30 days

Initial Evaluation

I. **Gilteritinib (Xospata)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of **relapsed/refractory FLT3-mutated acute myeloid leukemia** and all of the following are met:
      1. The disease is classified as relapsed/refractory AML **AND**
      2. Will not be used in combination with any other oncolytic medication; **AND**
      3. FLT3 mutation status has been detected by an FDA-approved test (e.g., LeukoStrat CDx FLT3 mutation Assay by Invivoscribe Technologies,Inc.)

II. Gilteritinib (Xospata) is considered investigational when used for all other conditions, including but not limited to:
   A. Gilteritinib (Xospata) as monotherapy or in combination (e.g., azacitidine) for newly diagnosed AML
   B. AML in the absence of FLT3 mutation
   C. AML in combination with other therapies in the relapsed/refractory setting

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 of 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., no signs of disease progression, no signs of unacceptable toxicity); **AND**
IV. Gilteritinib (Xospata) will not be used in combination with any other oncolytic medication

Supporting Evidence

I. The ADMIRAL trial only included adult patients and gilteritinib is only approved for treatment in adult patients who have relapsed or refractory AML with FLT3 mutations. The safety and efficacy of gilteritinib in the pediatric population has not been established, and clinical trials including pediatric patients are still ongoing at this time. Given the lack of safety and efficacy data in this patient population, use of gilteritinib is restricted to adults 18 years and older.
II. Many treatment options exist for AML. Initial and further line therapies in this setting are contingent upon patient specific characteristics, disease-risk, and cytogenetic stratification. Given the complexities involved with the diagnosis and management of AML, treatment with gilteritinib must be initiated and/or supervised by an oncologist or hematologist.
III. Gilteritinib (Xospata) was studied in a phase III, randomized controlled trial, which included 138 adult patients with relapse or refractory FMS-like tyrosine kinase 3 gene (FLT3) mutated AML against salvage chemotherapy (i.e., had not reached CR following treatment). The efficacy of XOSPATA was established on the basis of the rate of complete remission (CR)/CR with partial hematological recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence at the first interim analysis in the ADMIRAL trial (n=138). The final analysis of the ADMIRAL included 371 adult patients randomized 2:1 to receive gilteritinib 120mg daily or a prespecified chemotherapy regimen. Overall survival data were included in the final analysis, measured from the data of randomization until death by any cause. Patients randomized to the XOSPATA arm had significantly longer survival compared to the chemotherapy arm (HR 0.64; 95% CI: 0.49 – 0.83; 1-sided p-value: 0.0004), with median OS of 9.3 months vs 5.6 months for chemotherapy.
IV. Compared to salvage chemotherapy, gilteritinib had higher incidence of any, grade ≥3 adverse events, and serious adverse events for reported adverse events. Common adverse events of grade 3 or higher in the gilteritinib group were febrile neutropenia (45.9% vs 36.7%), anemia (40.7% vs 30.3%), and thrombocytopenia (22.8% vs 16.5%) for gilteritinib compared to salvage chemotherapy. In the Gilteritinib arm, 30.9% of patients experienced febrile neutropenia deemed as a serious adverse event, compared to 8.3% for chemotherapy. Due to the high incidence of any and serious adverse events, split fill management is required.
V. There were 251 deaths in the safety population of 355 patients, including 170 deaths among 246 patients (69.1%) in the gilteritinib group and 81 deaths among 109 patients (74.3%) in the chemotherapy group. In the intention-to-treat population, mortality at 30 days and at 60 days was 2.0% and 7.7%, respectively, in the gilteritinib group and 10.2% and 19.0%, respectively, in the chemotherapy group.
VI. Subjects included were adults with confirmed FLT3-mutated AML as detected by an FDA-approved test, (e.g., LeukoStrat® CDx *FLT3* Mutation Assay). Use of gilteritinib (Xospata) in

assigned subjects was as monotherapy only. Currently, there are no literature available on safety and efficacy outside of this setting.

VII. The NCCN guidelines for the treatment of AML was updated in March 2023, which recommends gilteritinib monotherapy for relapsed/refractor disease with FLT3 mutation at a category 1 recommendation. For patients that are not a candidate for intensive induction therapy with FLT3 mutated AML, gilterinib + azacitidine combination treatment is the only category 2B therapy, with other monotherapy and combination therapy regimens receiving category 2A recommendations (e.g., LDAC + ventoclax, or azacitidine monotherapy, decitabine monotherapy, sorafenib monotherapy, or azacitidine/decitabine + sorafenib). In the post allogeneic HCT, AML in remission with history of FLT3-ITD mutation setting, sorafenib is recommended (category 2A), while gilterinib (category 2B) due to a lack of safety and efficacy data supporting the use of gilteritinib in this setting.

Investigational or Not Medically Necessary Uses

I. Newly diagnosed AML
   A. There is lack of evidence for the use of gilteritinib (Xospata) as monotherapy in patients with newly diagnosed AML. The LACEWING Trial, a phase III, randomized, open-label study compared the efficacy and safety of gilteritinib with azacitidine against azacytidine alone in newly diagnosed AML patients with FLT3 mutation not eligible for intensive induction chemotherapy. The primary outcome was OS. At the interim analysis, the study failed to demonstrate a difference in median OS between the treatment arms for gilteritinib + azacitidine (9.82 months) versus azacitidine monotherapy (8.87 months) (HR, 0.916, 95% CI, 0.529-1.585; P=0.753), and the study was closed based on protocol-specified boundary for futility. The Median event-free survival was 0.03 months in both arms.

II. AML in the absence of FLT3 mutation
   A. Clinical trials have only evaluated gilteritinib (Xospata) in patients that have a confirmed FLT3 mutation by an FDA-approved test.

III. AML in combination with other therapies in the relapsed/refractory setting
   A. There is a lack of well-designed phase II/III clinical trials supporting the safety and efficacy of gilteritinib (Xospata) outside of the monotherapy in the relapsed/refractory setting. Clinical trials evaluating gilteritinib (Xospata) combination therapy are still ongoing. There is a Phase IB non-randomized, open label, single-arm trial accessing the safety and efficacy of venetoclax (Venclexta) in combination with gilteritinib (Xospata) in patients with R/R AML, however without a comparison arm to gilteritinib monotherapy, it is difficult to determine the safety and efficacy value of combination therapy versus monotherapy at this time.

** 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. Xospata [Prescribing Information]. Northbrook, Illinois: Astellas Pharma; November 2018.
2. NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 3.2023. National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed June 1, 2023.
3. Rydapt [Prescribing Information]. East Hanover, New Jersey: Novartis pharmaceuticals; June 2018.
4. ClinicalTrials.gov
5. Wang ES, Montesinos P, Minden MD, et al. Phase 3 trial of gilteritinib plus azacitidine vs azacitidine for newly diagnosed FLT3mut+ AML ineligible for intensive chemotherapy. *Blood*. 2022;140(17):1845-1857. doi:10.1182/blood.2021014586
6. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or Chemotherapy for Relapsed or Refractory *FLT3*-Mutated AML [published correction appears in N Engl J Med. 2022 May 12;386(19):1868]. *N Engl J Med*. 2019;381(18):1728-1740. doi:10.1056/NEJMoa1902688
7. Perl AE, Larson RA, Podoltsev NA, et al. Follow-up of patients with R/R FLT3-mutation-positive AML treated with gilteritinib in the phase 3 ADMIRAL trial. *Blood*. 2022;139(23):3366-3375. doi:10.1182/blood.2021011583
8. Daver N, Perl AE, Maly J, et al. Venetoclax Plus Gilteritinib for *FLT3*-Mutated Relapsed/Refractory Acute Myeloid Leukemia. *J Clin Oncol*. 2022;40(35):4048-4059. doi:10.1200/JCO.22.00602

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
Quizartunib (Brand)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with 7+3 induction and cytarabine consolidation

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence, renewal criteria language and formatting.	06/2023
Previous Reviews	01/2019; 02/2019

glasdegib (DAURISMO®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP206

Split Fill Management*

Description

Glasdegib (Daurismo) is an orally administered hedgehog pathway inhibitor that inhibits Smoothened proteins involved in hedgehog signal transduction. As a result, glasdegib reduces the amount of CD25+/CD33+ blasts in the bone marrow.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
glasdegib (Daurismo)	Acute myeloid leukemia, newly diagnosed	25 mg tablets	60 tablets / 30 days
		100 mg tablets	30 tablets / 30 days

Initial Evaluation

I. **Glasdegib (Daurismo)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
   B. A diagnosis of newly diagnosed acute myeloid leukemia (AML); **AND**
      1. Member is 75 years or older; **OR**
      2. Provider attests that the member has comorbidities that preclude intensive induction chemotherapy (e.g., baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatine clearance <30 mL/min); **AND**
      3. Treatment will be used in combination with low-dose cytarabine (LDAC)

II. Glasdegib (Daurismo) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute Myeloid Leukemia – Previously treated
   B. Monotherapy use or used in combination with azacitidine or decitabine

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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., became independent of red blood cell and platelet transfusion, or exhibited tumor response)

Supporting Evidence

I. Standard of care intensive induction chemotherapy for treatment of AML consists of a 7-day continuous infusion of cytarabine and daunorubicin and can induce complete response (CR) rates as high as ≥80% with a 5-year overall survival (OS) of ~40–50% in younger patients without adverse cytogenetic or molecular risk factors. Elderly or unfit patients tend to have poorer outcomes due to the inability to tolerate intensive therapy, deleterious genetic changes, comorbidities, or ineligibility for allogenic hematopoietic stem cell transplant.
II. Medical fitness is a key determinant of management of AML and influence the goals of care and choice of therapy. Determination of medical fitness is based on assessment of performance status using the Eastern Cooperative Oncology Group performance scale (ECOG PS) and physiological fitness (assessment of comorbid conditions, activities of daily living, cognition, etc. by the Charlson comorbidity index [CCI]). The ECOG PS ranges from 0-4, zero being fully active with no performance restrictions, and four being completely disabled, cannot carry out any self-care or totally confided to bed. The CCI predicts the ten-year mortality of a patient who has comorbid conditions. The maximum CCI score is 24 with three grades: 1-2 mild, 3-4 moderate, and ≥5 severe. Fitness categories fall into three groups: medically fit and able to tolerate intensive induction treatment for AML (ECOG PS 0-2 or CCI 0-2), medically unfit, but not frail and are unlikely to tolerate intensive antileukemic therapy (ECOG PS 3 or CCI 3), and frail, those whose comorbid conditions would not permit treatment (ECOG PS ≥3 or CCI ≥3).
III. Glasdegib (Daurismo) is FDA-approved, in combination with LDAC, for the treatment of newly diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
IV. Glasdegib (Daurismo) was studied in a multicenter, open-label, randomized study (BRIGHT AML 1003). Participants included were 55 years and older with newly diagnosed AML and met one of the following: at least 75 years old, severe cardiac disease, baseline ECOG PS of 2, or a baseline serum creatinine > 1.3 mg/dL. Participants were randomized 2:1 to receive glasdegib (Daurismo) 100mg daily with low-dose cytarabine 20mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle (N=77), or low-dose cytarabine alone (N=28) until disease progression or unacceptable toxicity. Both arms had similar baseline characteristics with a mean age of 76.5 years, mostly white male, and history of secondary AML (53%). The active arm had 41 participants (53%) and the cytarabine arm had 18 participants (47%) with ECOG PS score of 2. The study did not include patients with an ECOG PS of 3, severe renal, or hepatic impairment, all of which are comorbidities that would preclude use of intensive chemotherapy.

V. The primary endpoint was OS from the date of randomization to death from any cause with a mean follow-up of 20 months. The active arm had a median OS of 8.3 months (95% CI 4.4-12.2) and cytarabine arm 4.3 months (95% CI, 1.9-5.7), hazard ratio (HR) 0.46 (95% CI, 1.9-5.7), p=0.0002. The complete response rate (CR) in the active arm was 18.2% (95% CI, 10.3-28.6) and 2.6% (95% CI, 0.1-13.8) in the cytarabine group.

VI. Serious adverse events were reported in 79% of participants in the active arm with the most common adverse reactions being neutropenia (29%), pneumonia (23%), hemorrhage (12%), anemia (7%), and sepsis (7%). A total of 36% of participants receiving glasdegib (Daurismo) discontinued treatment due to pneumonia (6%), febrile neutropenia (4%), sepsis (4%), sudden death (2%), myocardial infarction (2%), nausea (2%), and renal insufficiency (2%).

VII. Glasdegib (Daurismo) has not been studied in patients with severe renal impairment or moderate-to-severe hepatic impairment. Glasdegib (Daurismo) can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and is not recommended for use during pregnancy.

VIII. NCCN guidelines preferred hypomethylating agents (HMA) (e.g. azacitidine, decitabine) plus venetoclax for treatment of AML in patients who are not candidates for intensive induction therapy. Preferred treatment includes azacitidine plus venetoclax (category 1) and decitabine and venetoclax (category 2A). Phase III trials demonstrated that azacitidine and decitabine are associated with greater overall survival (OS) compared to conventional care regimens (LDAC, intensive induction chemotherapy, or best supportive care). Other recommended treatment options include LDAC plus venetoclax, azacitidine or decitabine monotherapy, glasdegib plus LDAC, and best supportive care (category 2A).

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. Monotherapy use or used in combination with azacitidine or decitabine
   A. Monotherapy use or use in combination with azacitidine or decitabine is not supported within guidelines or clinical evidence. The clinical trial evaluating glasdegib and decitabine was terminated due to failure to accrue participants. BRIGHT AML 1012 (NCT02367456) was a multicenter open label phase 1b study that evaluated the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of glasdegib when combined with azacitidine in patients with previously untreated Higher Risk Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), or Chronic Myelomonocytic Leukemia (CMML). Overall response rates in the AML and MDS cohorts were 30.0% and 33.3%, respectively; 47.4% and 46.7% of patients who were transfusion dependent at baseline achieved independence. Median overall survival (95% confidence interval) was 9.2 (6.2-14.0) months and 15.8 (9.3-21.9) months.

**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. Iyer SG, Stanchina M, Bradley TJ, Watts J. Profile of Glasdegib for the Treatment of Newly Diagnosed Acute Myeloid Leukemia (AML): Evidence to Date. Cancer Manag Res. 2022;14:2267-2272. Published 2022 Aug 1.
2. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2018
3. Daurismo [prescribing information]. Pfizer Labs, Inc.: New York, NY. March 2023.
4. Venclexta [prescribing information]. Genentech: San Francisco, CA. November 2018.
5. U.S. Food and Drug Administration. FDA approves new treatment for patients with acute myeloid leukemia. Published November 21, 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm626443.htm
6. NCCN Clinical Practice Guideline in Oncology: Acute Myeloid Leukemia. Version 3.2023. National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Updated April 5, 2023.
7. Cortes, J. E., Heidel, F. H., Heuser, M., et al. A Phase 2 Randomized Study of Low Dose Ara-C with or without Glasdegib (PF-04449913) in Untreated Patients with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome. Blood, 128(22), 99. Accessed December 03, 2018.
8. Martinelli, G., Oehler, V. G., Papayannidis, C., et al. Treatment with PF-04449913, an oral smoothened antagonist, in patients with myeloid malignancies: a phase 1 safety and pharmacokinetics study. The Lancet Hematology, 2(8), e339-e346.
9. Erba, Harry P. "Finding the optimal combination therapy for the treatment of newly diagnosed AML in older patients unfit for intensive therapy." Leukemia research 39.2 (2015): 183-191.
10. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. Psychother Psychosom. 2022;91(1):8-35.
11. Sekeres MA, Schuster M, Joris M, et al. A phase 1b study of glasdegib + azacitidine in patients with untreated acute myeloid leukemia and higher-risk myelodysplastic syndromes. Ann Hematol. 2022;101(8):1689-1701.

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
venetoclax (Venclexta®)	Newly diagnosed acute myeloid leukemia (AML)
IDH inhibitors	Relapsed or refractory Acute Myeloid Leukemia (AML), Newly diagnosed AML, locally advanced or metastatic cholangiocarcinoma
midostaurin (Rydapt)	Acute Myeloid Leukemia (AML) newly diagnosed with FLT3 mutation, Systemic mast cell disease
azacitidine (Onureg®)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission

Policy Implementation/Update:

Action and Summary of Changes	Date
No clinical changes. Wording of comorbidities that may preclude newly diagnosed AML patients from intensive induction chemotherapy has been updated to improve flow and reduce misinterpretation. The supporting evidence has been updated to reflect current guideline recommendations and reflect pivotal trials. The reference section has been updated to include NCCN guidelines for AML and reflect changes.	06/2023
Policy created.	01/2019

Policy Type: PA Pharmacy Coverage Policy: UMP021

Description

Elagolix and relugolix are oral gonadotropin-releasing hormone (GnRH) antagonists.

Length of Authorization

- Initial: Three months
- Renewal:
  i. Elagolix (Orilissa) 150 mg: Up to 12 months; maximum total (lifetime) fills should not exceed #24 30-day fills
  ii. Elagolix (Orilissa) 200 mg: Up to three months; maximum total (lifetime) fills should not exceed #6 30-day fills
  iii. Elagolix/estradiol/norethindrone acetate (Oriahnn) and relugolix/estradiol/norethindrone (Myfembree): Up to 12 months; maximum total (lifetime) fills should not exceed #24 28-day fills

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
elagolix (Orilissa)	Moderate to severe pain associated with endometriosis	150mg tablets	30 tablets/30 days
		200mg tablets	60 tablets/30 days
elagolix/estradiol/ norethindrone acetate (Oriahnn)	Treatment of heavy menstrual bleeding associated with uterine fibroids	300 mg/1 mg/0.5 mg tablets	56 tablets/28 days
relugolix/estradiol/ norethindrone (Myfembree)	Heavy menstrual bleeding associated with uterine fibroids (leiomyoma) Moderate to severe pain associated with endometriosis	40 mg/1 mg/0.5 mg tablets	28 tablets/28 days

Initial Evaluation

I. **Elagolix (Orilissa), elagolix/estradiol/norethindrone acetate (Oriahnn) and relugolix/estradiol/norethindrone (Myfembree)** 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 obstetrician/gynecologist; **AND**
   C. Member does **not** have history of osteoporosis (defined as a T-score less than or equal to -2.5 or Z-score less than -1.5 at the lumbar spine, femoral neck or total hip); **AND**
   D. Provider attestation that the member has not previously been treated with a full course of a GnRH antagonist (i.e., Orilissa, Oriahnn, Myfembree); **AND**

E. A diagnosis of one of the following:
    1. **Moderate-to-severe pain associated with endometriosis; AND**
        i. Request is for elagolix (Orilissa) or relugolix/estradiol/norethindrone (Myfembree); **AND**
        ii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
            a. Nonsteroidal anti-inflammatory drugs (NSAIDs); **OR**
            b. Hormonal contraceptives (oral, IUD, implant, etc.); **AND**
        iii. If the request is for elagolix (Orilissa) and continued use of estrogen containing contraceptives is planned in combination, the provider acknowledges that the efficacy of both the contraceptive and elagolix (Orilissa) may be decreased (use of non-hormonal contraceptives is recommended); **OR**
    2. **Heavy menstrual bleeding associated with uterine fibroids; AND**
        i. Request is for elagolix/estradiol/norethindrone acetate (Oriahnn) or relugolix/estradiol/norethindrone (Myfembree); **AND**
        ii. At least one hormonal contraceptive (oral, IUD, implant, etc.) has been ineffective, not tolerated, or ALL are contraindicated; **AND**
        iii. Treatment with tranexamic acid has been ineffective, not tolerated, or is contraindicated

II. Elagolix and/or relugolix is considered investigational when used for all other conditions, including but not limited to:
    A. Polycystic ovary syndrome
    B. Fertility treatment

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**
III. Provider attestation that the member has not previously received treatment with a full course of a GnRH antagonist (i.e., Orilissa, Oriahnn, Myfembree); **AND**
IV. **Elagolix (Orilissa)**:
    A. Member has experienced a clinical improvement in pain symptoms relating to endometriosis; **AND**
        1. If the request is for elagolix (Orilissa) 150 mg; the member has not received treatment with elagolix (Orilissa) 150 mg for more than 24 months; **OR**
        2. If the request is for elagolix (Orilissa) 200 mg**;** the member has not received treatment with elagolix (Orilissa) 200 mg for more than 6 months; **OR**
V. **Elagolix/estradiol/norethindrone acetate (Oriahnn)**:
    B. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improved quality of life, etc.); **AND**

1. The member has not received treatment for more than 24 months

VI. Relugolix/estradiol/norethindrone (Myfembree):

C. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improved quality of life, etc.); **AND**

1. The member has not received treatment for more than 24 months

Supporting Evidence

I. Elagolix and Relugolix combination oral gonadotropin-releasing hormone (GnRH) antagonists have been evaluated in several clinical trials in adults. The safety and efficacy in pediatric patients have not been established and FDA approvals for these agents are limited to adult members.

II. Endometriosis and uterine fibroids are complex diseases and given the potential for long term side effects of GnRH antagonists, supervision of treatment/consultation by a gynecologist or obstetrician is required.

III. Clinical trials evaluating elagolix with or without estradiol/norethindrone excluded patients with a Z-score less than -1.5 at the lumbar spine, femoral neck, or total hip. Bone loss of more than 5% was seen in lumbar spine, total hip, and femoral neck within six months of treatment. Clinical trials evaluating relugolix/estardiol/norethindrone (Myfembree) excluded patients with Z-score less than -2.0 at the lumbar spine, femoral neck, or total hip. Bone loss of approximately 1% was seen in the lumbar spine within 6 months and consistent through 2 years of treatment. Bone loss studies have not yet been completed to evaluate elagolix (Orilissa) and elagolix/estradiol/norethindrone acetate (Oriahnn) in combination with bone loss prevention treatments.

IV. **Elagolix (Orilissa)** is an oral GnRH antagonist for the management of moderate to severe pain associated with endometriosis. The drug was studied in two randomized, double-blind, placebo-controlled, Phase 3, trials (Study EM-1 and Study EM-2; Elaris Endometriosis I and II).

- At three months, both elagolix (Orilissa) 150 mg and 200 mg regimens showed a higher proportion of responders compared to placebo. Both treatment arms showed statistically significant differences in greater mean decreases in non-menstrual pelvic pain scores from baseline at six months.
- The FDA-approved maximum duration of use for 150 mg tablets is 24 months, though clinical trials only studied up to 12 months. The FDA-approved maximum duration of use for 200 mg tablets is six months. These FDA maximum durations of treatment are recommended due to loss of bone marrow density as seen in clinical trials. Bone loss of more than 5% was seen in lumbar spine, total hip, and femoral neck within six months of treatment. Studies have not yet been completed to evaluate in combination with bone loss prevention treatments.
- Due to the mechanism of action, use of estrogen containing contraceptives are expected to reduce the efficacy of elagolix (Orilissa); likewise, use of elagolix (Orilissa) will reduce efficacy of estrogen containing oral contraceptives. To avoid drug interactions, use of non-hormonal contraceptives during treatment with elagolix (Orilissa) is recommended.

V. For the treatment of heavy menstrual bleeding associated with uterine fibroids there is a lack of randomized trial data demonstrating the effectiveness of medical therapies. Treatment options include hormonal contraceptives (oral, IUD, implant, etc.), ulipristal acetate (Ella), mifepristone

(Korlym, Mifeprex), GnRH agonists (leuprolide depot (Lupron), nafarelin acetate (Synarel), goserelin acetate (Zoladex), etc.), raloxifene (Evista), and danazol. GnRH agonists are an effective medical therapy but due to side effects are primarily used as preoperative therapy. Surgical treatment options are available, but often patients become incapable of reproduction.

VI. Uterine fibroids are commonly experienced by women that are premenopausal, and are associated with heavy menstrual bleeding, pain, and anemia. Management strategies for uterine fibroids include hysteroscopic fibroid resection, estrogen-progestin contraceptives, progestin-releasing intrauterine devices, progestin-only contraceptives, tranexamic acid, GnRH agonists (e.g., Lupron), GnRH antagonists (e.g., Oriahnn, Myfembree), uterine artery embolization, hysterectomy, and endometrial ablation.

VII. Treatment choice is dependent on fibroid size, patient age, fertility preference, symptoms, and other patient related factors. Hysterectomy is the only definitive cure, but myomectomy may be preferred for women with submucosal fibroids wishing to preserve the uterus. Medication therapy may be preferred for management to either prolong time to surgery or as preoperative treatment in preparation for surgery. Given the complex treatment choices and risks associated with each, therapy should be directed by or in consultation with a specialist.

VIII. The most common medication therapy utilized for the management of uterine fibroids includes estrogen-progestin contraceptives (e.g., pills, rings, patches) and progestin IUDs. These interventions do not change affect the pathology of the fibroids, but they are accepted as a standard management strategy to reduce the heavy menstrual bleeding. Tranexamic acid is a nonhormonal treatment that may be used during menstruation to reduce heavy bleeding.

IX. As the safety profiles often limit their use, GnRH agonists and antagonists are second-line medications. GnRH agonists (e.g., Lupron) are often used for a few months preoperatively to reduce fibroid size, or to bridge a patient into menopause. For GnRH antagonists, there are two products available: relugolix/estradiol/norethindrone (Myfembree), and elagolix/estradiol/norethindrone (Oriahnn). Acute tolerability is generally more favorable, but long-term safety and efficacy data are limited. Additionally, there is a known decrease in bone mineral density (BMD) which limits treatment duration. Furthermore, the safety of utilizing GnRH antagonists subsequently at their full FDA-approved duration is unknown, and would be expected to exacerbate the decrease in BMD.

X. For the treatment of pain associated with endometriosis there are no studies supporting one treatment, or treatment combination, over another. Treatment choice is based upon symptom severity, patient preferences, medication side effects, treatment efficacy, contraceptive needs, costs, and availability. Treatments commonly used first-line are NSAIDs and continuous hormonal contraceptives because these therapies are low-risk, have few side effects, and provide relief of symptoms for many women. Second-line treatments include GnRH agonists (leuprolide depot (Lupron), nafarelin acetate (Synarel), goserelin acetate (Zoladex), etc.), progestins, and danazol.

XI. **Elagolix/estradiol/norethindrone acetate (Oriahnn)** was evaluated in two six-month, randomized, double-blind, placebo-controlled, Phase 3 trials (Elaris UF-1 and Elaris UF-2) and one six-month, extension trial (Elaris UF-EXTEND). The primary efficacy outcome was the percentage of women who had menstrual blood loss (MBL) volume <80 mL during the final month and ≥ 50% reduction in MBL volume from baseline to the final month.

- In Elaris UF-1, the primary outcome was 68.5%, 84.1%, and 8.7% (p<0.001) for elagolix/estradiol/norethindrone acetate (Oriahnn) plus hormonal therapy, elagolix alone, and placebo, respectively. In Elaris UF-2, the primary outcome was 76.5%, 76.9%, 10.5% (p<0.001) for elagolix/estradiol/norethindrone acetate (Oriahnn), elagolix alone, and placebo, respectively. In Elaris UF-EXTEND, the primary outcome was 87.9% for elagolix/estradiol/norethindrone acetate (Oriahnn). The hormonal therapy that was used in combination with elagolix was estradiol/norethindrone (Activella, Amabelz, Combipatch, Lopreeza, Mimvey Lo, and Mimvey).
- The most common adverse events noted for elagolix/estradiol/norethindrone acetate (Oriahnn) were hot flashes, night sweats, nausea, and headache; however, elagolix/estradiol/norethindrone acetate (Oriahnn) had lower rates of hot flashes and night sweats compared to elagolix (Orilissa). Elagolix/estradiol/norethindrone acetate (Oriahnn) also had a reduced change from baseline in bone mineral density compared to elagolix (Orilissa). Elaris UF-1 had similar rates of discontinuation due to adverse events across all treatment arms; however, in Elaris UF-2, elagolix (Orilissa) had a discontinuation rate of 12.6% compared to 8.5% and 5.3% for elagolix/estradiol/norethindrone acetate (Oriahnn) and placebo, respectively. Elaris UF-EXTEND had lower rates of adverse events in the final six months compared to Elaris UF-1 and UF-2.
- The FDA has indicated that use of Oriahnn should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

XII. **Relugolix/estradiol/norethindrone (Myfembree)** was evaluated in the setting of heavy menstrual bleeding associated with uterine fibroids (leiomyoma) and moderate to severe pain associated with endometriosis.

- **Uterine Fibroids**: Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two Phase 3, double-blind, randomized, placebo-controlled trials over 24 weeks (LIBERTY 1 and LIBERTY 2). Therapy was evaluated in premenopausal women with heavy menstrual bleeding and diagnosis of uterine fibroids, confirmed via ultrasonography. Patients with osteoporosis or osteopenia were excluded.
- Primary outcome: percentage of participants with treatment response (blood loss volume < 80 mL and ≥ 50% reduction in volume). Secondary outcomes: proportion of patients reaching amenorrhea, change in blood loss volume, pain, distress from bleeding and pelvic discomfort, and participants that had a change in hemoglobin of 2 g/dL or more in those that had anemia at baseline. These outcomes were statistically and clinically significant over placebo. In clinical trials, relugolix/estradiol/norethindrone (Myfembree) did not reduce uterine fibroid volume.
- Relugolix was also evaluated as monotherapy in a randomized, blinded, non-inferiority (NI) trial vs. leuprorelin (Lupron). Relugolix showed to be NI to leuprorelin (Lupron) in the following outcomes: blood loss, amenorrhea, uterine volume, fibroid volume, hemoglobin improvement, pain, and quality of life. Estrogenic AE and decrease in BMD were notable; thus, the manufacturer is pursuing combination therapy with estradiol and norethindrone to mitigate these concerns. A limitation of the trial is the majority of patients received leuprorelin (Lupron) 1.88 mg, rather than the standard U.S. dose of

3.75 mg. Comparative safety and efficacy data to the 3.75 mg dose of leuprorelin (Lupron) is currently unknown.

- **Endometriosis:** Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two replicate, phase 3, randomized, double-blind, placebo-controlled trial over 24 weeks (SPIRIT 1 and SPIRIT 2). Therapy was evaluated in pre-menopausal women aged 18 – 50 years with moderate to very severe dysmenorrhea and non-menstrual pelvic pain associated with endometriosis. Patients were excluded from the trial if they had a history of Z-score consistent with osteoporosis or osteopenia.
- The co-primary outcomes were the proportion of responders based on dysmenorrhea NRS score and non-menstrual pelvic pain (NMPP) NRS score at the end of treatment. In both trials, relugolix/estradiol/norethindrone (Myfembree) demonstrated a statistically significant benefit in dysmenorrhea and NMPP compared to placebo. In SPIRIT 1, 75% of patients in the relugolix-CT group and 27% of patients in the placebo group were considered dysmenorrhea responders (95% CI 39.3-56.0; p<0.0001) while 59% of patients in the relugolix-CT group and 40% of patients in the placebo group were considered NMPP responders (95% CI 9.5-28.2; p<0.0001). In SPIRIT 2, 75% of patients in the relugolix-CT group and 30% of patients in the placebo group were considered dysmenorrhea responders (95% CI 36.2-53.5; p<0.0001) while 66% of patients in the relugolix-CT group and 43% of patients in the placebo group were considered NMPP responders (95% CI 14.0-32.8; p<0.0001).
- An extension trial (SPIRIT LTE) was conducted to assess the long-term efficacy and safety of relugolix with estradiol/norethindrone (relugolix-CT) for the treatment of moderate to severe pain associated with endometriosis up to 104 weeks. Participants were required to have completed 24 weeks of participation in either SPIRIT 1 or SPIRIT 2; all eligible patients were assigned to receive relugolix-CT during the 80-week, open-label treatment period. SPIRIT LTE used the same co-primary endpoints as the SPIRIT 1 and SPIRIT 2 trials. For the co-primary endpoint of dysmenorrhea responders, at the end of 104 weeks of treatment, 84.8% and 83.0% of patients in the relugolix-CT and delayed relugolix-CT groups, respectively were considered dysmenorrhea responders; at the end of 80 weeks of treatment, 80.4% of patients who initially received placebo were considered dysmenorrhea responders. For the co-primary endpoint of NMPP responders, 75.8% of patients in the relugolix-CT group and 71.7% of patients in the delayed relugolix-CT group were considered NMPP responders; in patients initially treated with placebo, 73.1% were considered NMPP responders at week 52. No new safety signals were identified during the long-term extension period.

XIII. In both the LIBERTY and SPIRIT trials, rate of overall AEs was consistent for placebo and active therapy. No deaths occurred in the trials and serious AEs were rare. In the LIBERTY trials, there were a few cases of ankle fracture in those that received relugolix/estradiol/norethindrone (Myfembree). At week 24 the BMD at lumbar spine and total hip were similar between groups. AE leading to treatment discontinuation occurred in 4-11% of patients. Common AE included the following: hot flash (6-11% vs. 4-8% for placebo) and hypertension (5% vs. 0% for placebo). Other AEs that occurred in ≥ 5% of patients included headache, arthralgia, cough, nausea, URI, nasopharyngitis, fatigue, and anemia. Long term safety is currently unknown but will be better understood with results from long-term safety extension trials. The FDA has indicated that use

of Myfembree should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

XIV. Elagolix (Orilissa), elagolix/estradiol/norethindrone acetate (Oriahnn), and relugolix/estradiol/norethindrone (Myfembree) are contraindicated in pregnant patients due to an increased risk of early pregnancy loss.

Investigational or Not Medically Necessary Uses

I. Elagolix and/or relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Polycystic ovary syndrome
   B. Fertility treatment

References

1. Orilissa [Prescribing Information]. North Chicago, IL: AbbVie Inc.; February 2021.
2. Oriahnn [Prescribing Information]. North Chicago, IL: AbbVie Inc.; August 2021.
3. Myfembree [Prescribing Information]. Patheaon Inc. Mississauga, Ontario, Canada. Myovant Sciences, Brisband, CA. September 2022.
4. UpToDate, Inc. Endometriosis: Treatment of pelvic pain. UpToDate [database online]. Waltham, MA. Updated July 29, 2019.
5. UpToDate, Inc. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women. UpToDate [database online]. Waltham, MA. Updated July 11, 2019.
6. Taylor HS, Giudice LC, Lessey BA et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377:28-40. doi: 10.1056/NEJMoa1700089.
7. UpToDate, Inc. Overview of treatment of uterine leiomyomas (fibroids). UpToDate [database online]. Waltham, MA. Updated November 11, 2019.
8. Lupron Depot [Prescribing Information]. Abbvie Inc. Chicago, IL. January 2019.
9. Gillispie V, Muneyyirci-Delale O, Kim J, Liu R, et al. Up to 12 months of efficacy and safety of elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroids. Presented at the American Association of Gynecologic Laparoscopists, November 9-13, 2019; Vancouver, Canada.
10. Schlaff W, Al-Hendy A, Barnhart K, et al. Elagolix Reduced Heavy Menstrual Bleeding with Uterine Fibroids: Primary, 6-month, Phase 3 Results. Presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists, May 3-6, 2019; Nashville, Tennessee, USA.
11. Bradley L, Feinberg E, Liu R, et al. Elagolix Treatment in Women with Uterine Fibroids: Secondary, 6-Month, Phase 3 Efficacy Results. Presented at the 2019 American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting, May 3-6, 2019; Nashville, Tennessee, USA.
12. Giudice LC, As-Sanie S, Ferreira JCA, et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomized, double-blind, studies (SPIRIT 1 and 2). Lancet 2022; 399: 2267-79.

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

relugolix (Orgovyx™)	Prostate cancer
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
Criteria updated to include Myfembree for the indication uterine fibroids and moderate to severe pain with endometriosis; Changed policy name to 'GnRH Antagonists in Gynecologic Conditions'.	11/2022
Criteria updated to require specialist prescriber, removal of check on pregnancy status and menopausal status, and addition of assessment for prior use of GnRH antagonist relugolix. Supporting evidence updated, and format of policy updated to follow new standards. Experimental and investigational section added.	05/2021
Removed criteria: "Must be used in combination with an estradiol/norethindrone acetate product (Activella, Combipatch, Mimvey Lo, etc.)" from the indication heavy menstrual bleeding associated with uterine fibroids	12/2020
Added criteria for treatment of heavy menstrual bleeding associated with uterine fibroids, added requirements for premenopause and confirmation member is not pregnant. Also added NSAIDS as an option for trial and failure for pain associated with endometriosis.	12/2019
Transition from criteria to policy	09/2019
Criteria created	10/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP092

Description

The listed treatments are synthetic gonadotropin-releasing hormone (GnRHs) analogs that exhibit a potent reversible inhibition of gonadotropin secretion through suppression of testicular and ovarian steroidogenesis.

Length of Authorization and Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit	Duration of approval
nafarelin (Synarel)	Endometriosis	2 mg/mL nasal spray	16 mL/30 days	6 months
	Central Precocious Puberty		40 mL/30 days	6 months
leuprolide acetate (Lupron)	Central Precocious Puberty	1 mg/0.2mL kit	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	Endometriosis, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	3.75 mg/syringe kit	1 syringe kit/30 days	6 months for all indications EXCEPT - 3 months for uterine leiomyoma -2 months for Endometrial Thickness
	Advanced Prostate Cancer, Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Advanced Prostate Cancer, Advanced Breast Cancer, Endometrial Thickness, Uterine leiomyoma, Central Precocious Puberty, Gender Dysphoria	11.25 mg/syringe kit	1 syringe kit/90 days	6 months for all indications EXCEPT - 3 months for Uterine Leiomyoma -2 months for Endometrial Thickness
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	6 months

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

	Advanced Prostate, Cancer Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/120 days	6 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide acetate (Lupron Depot-Ped)	Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	11.25 mg/syringe kit	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months
	Central Precocious Puberty	15 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/90 days	6 months
	Central Precocious Puberty	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide acetate (Eligard)	Advanced Prostate Cancer	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	6 months
	Advanced Prostate Cancer	30 mg/syringe kit	1 syringe kit/120 days	6 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide-norethindrone (Lupaneta)	Endometriosis	3.75-5 mg/syringe	1 syringe kit/30 days	6 months
	Endometriosis	11.25-5 mg/syringe	1 syringe kit/90 days	6 months
Renewal				
nafarelin (Synarel)	Central Precocious Puberty	2 mg/mL nasal spray	40 mL/30 days	6 months
leuprolide acetate	Central Precocious Puberty	1 mg/0.2mL kit (each kit contains 2.8 mL of leuprolide acetate and 14 disposable syringes)	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	Endometriosis, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	3.75 mg/syringe kit	1 syringe kit/30 days	- 12 months for Advanced Breast Cancer and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal allow**) - NO RENEWAL for Uterine

				leiomyoma and Endometrial Thickness
	Advanced Prostate Cancer, Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	12 months
	Advanced Prostate Cancer, Advanced Breast Cancer, Endometrial Thickness, Uterine leiomyoma, Central Precocious Puberty, Gender Dysphoria	11.25 mg/syringe kit	1 syringe kit/90 days	- 12 months for Advanced Breast Cancer, Central Precocious Puberty, and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal**) - NO RENEWAL for Uterine leiomyoma and Endometrial Thickness
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	12 months
	Advanced Prostate, Cancer Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/120 days	12 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	12 months
Leuprolide acetate (Lupron Depot-Ped)	Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	11.25 mg/syringe kit	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months
	Central Precocious Puberty	15 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/90 days	6 months
	Central Precocious Puberty	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide acetate (Eligard)	Advanced Prostate Cancer	7.5 mg/syringe kit	1 syringe kit/30 days	12 months
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	12 months

	Advanced Prostate Cancer	30 mg/syringe kit	1 syringe kit/120 days	12 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	12 months
Leuprolide-norethindrone (Lupaneta)	Endometriosis	3.75-5 mg/syringe	1 syringe kit/30 days	6 months
	Endometriosis	11.25-5 mg/syringe	1 syringe kit/90 days	6 months (**MAX #1 renewal allow**)

Initial Evaluation

I. **Synthetic gonadotropin-releasing hormones (GnRHs)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a gynecologist, endocrinologist, or oncologist; **AND**
   B. A diagnosis of one of the following:
      1. **Endometriosis**; **AND**
         i. Member is 18 years of age or older; **AND**
         ii. Member requires pain relief and reduction of endometriotic lesions; **AND**
         iii. Treatment with a hormonal contraceptive has been ineffective, contraindicated, or was not tolerated; **AND**
         iv. The request is for Lupron Depot (3.75 mg, 11.25 mg), Synarel, OR Lupaneta; **OR**
      2. **Uterine leiomyoma (fibroids); AND**
         i. Member is 18 years of age or older; **AND**
         ii. The diagnosis of uterine leiomyoma has been confirmed by ultrasound or hysteroscopy; **AND**
         iii. Member requires therapy for anemia associated with preoperative management (e.g., hysterectomy, uterine artery embolization, myomectomy, hysteroscopy, etc.) of uterine leiomyoma; **AND**
         iv. Member will be on iron therapy concomitantly; **AND**
         v. The request is for Lupron Depot (3.75 mg, 11.25 mg); **OR**
      3. **Central Precocious Puberty (CPP)**; **AND**
         i. Documented onset of secondary sexual characteristics (e.g., genital maturation, pubic hair growth, and/or menses in female); **AND**
            a. Symptom onset before 8 years of age for FEMALE, 9 years of age for MALE; **AND**
         ii. FEMALE member is less than 11 years of age; MALE member is less than 12 years of age; **AND**
         iii. Member has clinical diagnosis of CPP confirmed by a pubertal response to a GnRH stimulation test or a pubertal basal level of luteinizing hormone (LH); **AND**
         iv. Provider attestation that the member has bone age advanced at least one year beyond chronological age; **OR**

4. **Advanced prostate cancer; AND**
    i. The request is for Lupron-Depot, or Eligard; **OR**
5. **Advanced breast cancer in premenopausal women; AND**
    i. The request is for Lupron-Depot 11.25 mg; **OR**
6. **Reduction of endometrial thickness prior to endometrial ablation; AND**
    i. The request is for Lupron Depot (3.75 mg, 11.25 mg), **OR**
7. **Gender Dysphoria**

II. Gonadotropin-releasing hormone (GnRH) analogs are considered not medically necessary when criteria above are not met and/or when used for:
    A. In vitro fertilization
    B. Premenstrual syndrome

Renewal Evaluation

I. 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**
II. 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**
III. A diagnosis of one of the following:
    A. Endometriosis; **AND**
        1. Member is responding positively to therapy (e.g., pain relief and reduction of endometriotic lesions); **AND**
        2. Provider attests that the member's bone mineral density has been assessed and has been deemed appropriate to continue GnRH therapy; **AND**
        3. The total duration of treatment with a GnRH analog has not exceeded a total of 12 months; **AND**
        4. The request is for leuprolide acetate (Lupron Depot) in combination with norethindrone, or Lupaneta; **OR**
    B. Central Precocious Puberty (CPP); AND
        1. Member is responding positively to therapy (e.g., lack of progression or stabilization of secondary sexual characteristics, decrease in growth rate, decrease in bone age to chronological age); **AND**
        2. Female member is less than 11 years of age; **OR**
            i. Male member is less than 12 years of age; **OR**
    C. Advanced prostate cancer; AND
        1. Provider attests that member has exhibited improvement in or stability of disease symptoms; **OR**
    D. Advanced breast cancer in premonopausal women; **AND**
        1. Provider attests that member has exhibited improvement in or stability of disease symptoms; **OR**
    E. Gender Dysphoria; AND
        1. A renewal approval of 12 months is allowed

Supporting Evidence

I. In clinical trials, leuprolide acetate (Lupron Depot), when compared to danazol 800 mg per day, significantly reduced symptoms of endometriosis (e.g., pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and induced laparoscopic improvement; however, due to decrease in bone mineral density, the total duration of therapy with leuprolide acetate for depot suspension should not exceed 12 months. If retreatment is needed after the initial six months, an addition of hormone therapy with norethindrone acetate is recommended. Clinical studies demonstrated that concurrent norethindrone acetate and calcium supplementation daily with leuprolide acetate (Lupron Depot) have shown to significantly reduce the loss of bone mineral density that occurs with GnRH treatment, without compromising the efficacy of relieving symptoms of endometriosis.

II. In a study, women with stage III-IV endometriosis were randomized to receive either laparoscopic surgery first followed by 6 months of nafarelin (Synarel) 200 mcg twice daily followed by a second-look laparoscopy (n=28) or no initial surgical procedure with nafarelin (Synarel) 200 mcg twice daily followed by a second-look laparoscopy with appropriate surgery (n=25). There was no difference in efficacy. Additionally, per label, safety and efficacy has not been established beyond 6 months.

III. In a randomized study, leuprolide acetate (Lupron depot) plus iron demonstrated clinical response (HCT of 36% or greater and Hb of 12 g/dL or greater) compared with iron alone at week 4 (40% vs 17%), week 8 (71% vs 39%), and week 12 (75% vs 49%). In the leuprolide acetate (Lupron depot) arm: excessive vaginal bleeding decreased in 80% of patients at 3 months; uterine and myoma volume decreases of 25% or greater occurred in 60% and 54% of patients, respectively; and mean fibroid diameter decreased from 6.3 cm to 5.6 cm. The use of leuprolide acetate (Lupron depot) for uterine leiyomyoma should not exceed an FDA max of 3 months therapy.

IV. Precocious puberty is defined as the onset of secondary sexual development before the age of eight years in females and nine years in males. Central precocious puberty (CPP), also known as gonadotropin-dependent precocious puberty or true precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis. CPP is characterized by sequential maturation of breasts and pubic hair in females, and maturation of the testes, penis, and pubic hair in males. Average age of puberty onset in females is 11 and 12 in males. The decision to discontinue treatment factors in the patient's bone age and height balanced with a desire to have pubertal progression with their peers.

V. GnRH stimulation tests have been the gold standard for confirmation of CPP diagnosis. However, new studies support the use of pubertal basal LH levels in diagnosis. The American Family Physician and Gonadotropin-Releasing Hormone Analogs in Children guidelines support use of basal LH levels to confirm the diagnosis of CPP after onset of symptoms. One study attempted to diagnose young girls with CPP based off pubertal basal LH levels. In over 90% of instances, basal LH levels were able to differentiate prepubertal patients from those with CPP using third-generation assays. The basal LH level threshold to diagnose CPP has not been definitively set, but a typical threshold of 0.3 U/L is used.

VI. Patients with CPP typically demonstrate early bone maturation and accelerated growth. Height velocity is considered accelerated if it exceeds 6 cm per year. As bones mature, CPP could lead to early closure of epiphysis, eventually resulting in a decreased adult height. The decision to

treat is based on pubertal progression (sexual maturation), height velocity, and rate of bone age advancement. The goal of GnRH treatment is preservation of height potential and growth to normal adult height and to address the psychosocial impact of early entry into puberty.

VII. MRI imaging is completed to rule out intracranial pathology such as hamartomas (tumor-like growth), CNS tumors, arachnoid cysts, and other lesions. Imaging can be used to identify the cause of CPP to determine if other treatments are needed. The American Academy of Pediatrics, American Family Physician, and European Society for Paediatric Endocrinology have released consensus statements that brain imaging should be performed in all boys and girls who are 6 years or younger. However, recommendations were also given to discuss the pros and cons of MRI scanning with the parents to assist in making an informed decision. Intracranial pathology occurs in up to 38% of boys and up to 6.3% in girls with CPP. A meta-analysis of CPP MRI findings found that only 1.6% of girls had CNS abnormalities required an intervention. Investigators suggest there is a lower incidence of tumors in girls older than 6 years and imaging above 6 years old will likely lead to incidental positive findings not related to CPP. Ultimately, treatment for CPP with a GnRH agent will occur independent of imaging or the presence of a tumor. Therefore MRI/imaging is not required for coverage of GnRH therapy.

VIII. In an open-label study, nafarelin acetate (Synarel) for the treatment of central precocious puberty in children demonstrated a growth rate reduction from 11.5 cm/year to 5.8 cm/year after 6 months of therapy.

IX. In open-label studies, monthly or once every 3 months of leuprolide acetate administration in children with central precocious puberty naïve to GnRH therapy demonstrated clinical and physical signs of puberty suppression. These clinical/physical signs include stopped or regressed secondary sexual characteristics, significantly improved mean height standard deviation for bone age, and suppressed luteinizing hormone and follicle stimulating hormone.

X. In an open-label, non-comparative, multicenter clinical trial, leuprolide acetate (Lupron depot) demonstrated a reduction and maintenance in serum testosterone level to castrate range (≤50 ng/dL). In the study, serum testosterone suppressed to the castrate range within 30 days of the initial depot injection in 94% (51/54) of patients for whom testosterone suppression was achieved (2 patients withdrew prior to onset of suppression) and within 66 days in all 54 patients. In a separate open-label study (AGL9904), leuprolide acetate (Eligard) 7.5 mg, 22.5 mg, 30 mg and 45 mg demonstrated castration suppression and maintenance.

XI. Multiple professional organizations, including ESHRE, NICE, ASRM, and ACOG, conclude that both combined hormonal contraceptives (CHCs) and progestin-only contraceptives (POCs), irrespective of hormone formulation or route of administration, are effective for managing endometriosis-associated symptoms. Current evidence does not support the superiority of one hormonal method over another. Either CHC or POC formulations, including oral pills, vaginal rings, transdermal patches, demedroxyprogesterone (DMPA) injections, implants and levonorgestrel intrauterine devices (LNG-IUDs) are appropriate treatment options. Clinical decision-making should be individualized, aligning contraceptive choice with patient preferences and clinical context.

- The PRE-EMPT trial, a three-year, open-label RCT (N=405), compared POCs (LNG-IUD or DMPA; n = 205) with CHCs (oral pills; n=200) using the EHP-30 questionnaire to assess pain outcomes. No statistically significant difference was observed between groups at three years (mean difference: -0.8; 95% CI: -5.7 to

4.2; p = 0.76), with both arms achieving a 40% reduction in pain scores from baseline.

- A meta-analysis of seven RCTs (N=948) comparing POCS (LNG-IUD or DMPA) to CHCs in women with endometriosis reported no significant differences in standardized mean differences (SMDs) for pelvic pain (SMD: 0.02; 95% CI: -0.37 to 0.40;p = 0.09; I2 = 66.7%), dysmenorrhea (SMD: 0.00; 95% CI: -0.19 to 0.19), or dyspareunia (SMD: 0.21; 95% CI: -0.04 to 0.85; p=0.52; I2 = 81.4%).

Investigational or Not Medically Necessary Uses

I. In vitro fertilization
   A. This is an excluded indication per the plan benefit.
II. Premenstrual syndrome
   A. There is currently insufficient evidence regarding safety and/or efficacy with leuprolide acetate in this setting.

References

1. Synarel [Prescribing Information]. New York, NY: G.D. Searle, LLC. May 2017.
2. Lupron Depot [Prescribing Information]. North Chicago, IL: Abbvie, Inc. June 2014, April 2018.
3. Lupron Depot-ped [Prescribing Information]. North Chicago, IL: Abbvie, Inc. August 2011.
4. Eligard [Prescribing Information]. Fort Collins: CO. Sanofi-Aventis U.S., LLC. 2010.
5. Houk CP, Kunselman AR, Lee PA. Adequacy of a single unstimulated luteinizing hormone level to diagnose central precocious puberty in girls. Pediatrics. 2009;123(6):e1059-e1063.
6. Heo S, Lee YS, Yu J. Basal serum luteinizing hormone value as the screening biomarker in female central precocious puberty. Ann Pediatr Endocrinol Metab. 2019;24(3):164-171.
7. Chen M, Eugster EA. Central Precocious Puberty: Update on Diagnosis and Treatment. Paediatr Drugs. 2015;17(4):273-281. doi:10.1007/s40272-015-0130-8
8. Fuqua JS. Treatment and outcomes of precocious puberty: an update. J Clin Endocrinol Metab. 2013;98(6):2198-2207.
9. Eugster EA. Treatment of Central Precocious Puberty. J Endocr Soc. 2019;3(5):965-972. Published 2019 Mar 28.
10. Latronico AC. Challenges in monitoring GnRH analog treatment in central precocious puberty. *Arch Endocrinol Metab*. 2020;64(2):103-104.
11. Kaplowitz P, Bloch C, the SECTION ON ENDOCRINOLOGY. Evaluation and Referral of Children With Signs of Early Puberty. Pediatrics. 2016;137(1):e20153732
12. Bangalore Krishna K, Fuqua JS, Rogol AD, et al. Use of Gonadotropin-Releasing Hormone Analogs in Children: Update by an International Consortium. Horm Res Paediatr. 2019;91(6):357-372.
13. Kaplowitz PB. Do 6-8 year old girls with central precocious puberty need routine brain imaging?. *Int J Pediatr Endocrinol*. 2016;2016:9.
14. Edi R, Cheng T. Endometriosis: Evaluation and Treatment. *Am Fam Physician. 2022;106(4):397-404.*
15. ESHRE Endometriosis Guideline Group. ESHRE guidelines: endometriosis. www.eshre.eu. February 2, 2022. Accessed July 15, 2025. https://www.eshre.eu/Guideline/Endometriosis
16. Endometriosis: diagnosis and management. London: National Institute for Health and Care (NICE); November 11, 2024.
17. Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: a committee opinion. *Fertile Steril.* 2014;101(4):927-935.
18. Practice bulletin no. 114: management of endometriosis. *Obstet Gynecol.* 2010;116(1):223-236
19. ACOG Committee Opinion No. 760: Dysmenorrhea and Endometriosis in the Adolescent. *Obstet Gynecol. 2018;132(6):249-258.*
20. Cooper KG, Bhattacharya S, Daniels JP, et al. Long acting progestogens versus combined oral contraceptive pill for preventing recurrence of endometriosis related pain: the PRE-EMPT pragmatic, parallel group, open label, randomised controlled trial. *BMJ.* 2024;385:e079006. Published 2024 May 15.

21. De Souza Gaio G, Kemczenski F, Fernandes Oliveria Amador W, Farias CF, Chagas J. Clinical effectiveness of progestogens compared to combined oral contraceptive pills in the treatment of endometriosis: A systematic review and meta-analysis. *Eur J Obstet Gynecol Reprod Biol.* 2025;306:219-225.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy criteria and supporting evidence to allow use of any hormonal contraception formulation prior to use of GnRH therapy for the treatment of endometriosis.	08/2025
Added mew strength of Lupron Depo peds 45 mg syringe kit	05/2023
Addition of CPP indication to the Lupron Depot injection products with corresponding strengths of Lupron Depot Ped. Updated criteria for central precocious puberty. Changed wording in the age criteria to specify "onset of symptoms" before specified age. Included basal serum LH levels in addition to GnRH stimulation test required for confirmation of diagnosis. Removed lines "beta human chorionic gonadotropin (HCG) level and adrenal and pelvic ultrasound or testicular ultrasound" as tests are specifically performed in the peripheral setting. Added evidence to support changes. Removed criteria requiring imaging prior to treatment with GnRH analogues. Updated supporting evidence with disease state background and guideline recommendations for diagnosis and treatment.	05/2022
Criteria transitioned into policy format. With the following updates made: added supporting evidence, added indications that are medically not necessary, added renewal criteria, limit renewal for endometriosis to a total duration of 12 months, limit initial approval for uterine leiomyoma to 3 months per FDA max, require bone mineral density evaluation upon renewal for the treatment of endometriosis, require concomitant iron therapy for uterine leiomyoma indication, updated Lupron-depot strength for advanced breast cancer, and no renewal for uterine leiyomyoma and endometrial thickness.	10/2019
Previous reviews	08/2017
Policy created	10/2014

Growth Hormone, Human

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP126

Description

Somatropin and somapacitan are purified polypeptide hormones of recombinant DNA origin. Somatropin is comprised of amino acids in a sequence identical to that of human growth hormone. Somapacitan includes a single substitution in the amino acid backbone to which an albumin-binding moiety is attached; it is otherwise an identical amino acid sequence to human growth hormone. Human growth hormone stimulates growth of linear bone, skeletal muscle, and organs, and stimulates erythropoietin which increases red blood cell mass, exerts both insulin-like and diabetogenic effects, and enhances the transmucosal transport of water, electrolytes, and nutrients across the gut. In short-bowel syndrome, growth hormone may directly stimulate receptors in the intestinal mucosa or indirectly stimulate the production of insulin-like growth factor-I which is known to mediate many of the cellular actions of growth hormone.

Length of Authorization

- Initial: Six months
  - i. AIDS wasting syndrome: three months only
  - ii. Short bowel syndrome: One month only
  - iii. All other indications: Six months
- Renewal: 12 months
  - i. AIDS wasting syndrome: three months only
  - ii. Short bowel syndrome: no renewal allowed
  - iii. All other indications: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
somatropin (Genotropin)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Prader-Willi syndrome • Small for gestational age • Turner syndrome	5 mg/mL cartridge	Pediatric GHD: 0.24 mg/kg/week Adult GHD: 0.08 mg/kg/week Idiopathic short stature: 0.47 mg/kg/week Prader-Willi syndrome: 0.24 mg/kg/week Small for gestational age: 0.48 mg/kg/week Turner syndrome:
		12 mg/mL cartridge	
somatropin (Genotropin MiniQuick)		0.2 mg/0.25 mL syringe	
		0.4 mg/0.25 mL syringe	
		0.6 mg/0.25 mL syringe	
		0.8 mg/0.25 mL syringe	
		1 mg/0.25 mL syringe	
		1.2 mg/0.25 mL syringe	
		1.4 mg/0.25 mL syringe	
		1.6 mg/0.25 mL syringe	
		1.8 mg/0.25 mL syringe	
		2 mg/0.25 mL syringe	

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ArrayRx administered by moda HEALTH

			0.33 mg/kg week
somatropin (Humatrope)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency • Small for gestational age • Turner syndrome	5 mg vial	Pediatric GHD: 0.3 mg/kg/week Adult GHD: 0.0875 mg/kg/week (0.0125 mg/kg/day) Idiopathic short stature: 0.37 mg/kg/week SHOX deficiency: 0.35 mg/kg/week Small for gestational age: 0.47 mg/kg/week Turner syndrome: 0.375 mg/kg week
		6 mg cartridge	
		12 mg cartridge	
		24 mg cartridge	
somatropin (Norditropin FlexPro)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Noonan syndrome • Prader-Willi syndrome • Small for gestational age • Turner syndrome	5 mg/1.5 mL pen injector	Pediatric GHD: 0.24 mg/kg/week Adult GHD: 0.112 mg/kg/week (0.016 mg/kg/day) Idiopathic short stature: 0.47 mg/kg/week Noonan syndrome: 0.46 mg/kg/week Prader-Willi syndrome: 0.24 mg/kg/week Small for gestational age: 0.47 mg/kg/week Turner syndrome: 0.47 mg/kg week
		10 mg/1.5 mL pen injector	
		15 mg/1.5 mL pen injector	
		30 mg/3 mL pen injector	
somatropin (Nutropin AQ)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults	5 mg/2 mL pen injector	Pediatric GHD: 0.3 mg/kg/week Adult GHD: <u>Age 18-35 years</u> 0.175 mg/kg/week

	• Growth failure associated with chronic renal insufficiency (CRI) • Idiopathic short stature • Turner syndrome	10 mg/2 mL pen injector	(0.025 mg/kg/day) <u>Age >36 years</u> 0.0875 mg/kg/week (0.0125 mg/kg/day) Chronic Renal Insufficiency: 0.35 mg/kg/week Idiopathic short stature: 0.3 mg/kg/week Turner syndrome: 0.375 mg/kg week
		20 mg/2 mL pen injector	
somatropin (Omnitrope)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Prader-Willi syndrome • Small for gestational age • Turner syndrome	5.8 mg vial	Pediatric GHD: 0.24 mg/kg/week Adult GHD: 0.08 mg/kg/week Idiopathic short stature: 0.47 mg/kg/week Prader-Willi syndrome: 0.24 mg/kg/week Small for gestational age: 0.48 mg/kg/week Turner syndrome: 0.33 mg/kg week
		5 mg/1.5 mL cartridge	
		10 mg/1.5 mL cartridge	
somatropin (Saizen)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults	5 mg vial	Pediatric GHD: 0.18 mg/kg/week Adult GHD: 0.07 mg/kg/week (0.01 mg/kg/day)
		8.8 mg vial	
somatropin (Saizen Click Easy)		8.8 mg/1.51 mL cartridge	
somatropin (Saizenprep)		8.8 mg cartridge	
somatropin (Serostim)	Wasting or cachexia associated with HIV	4 mg vial	28 vials/28 days
		5 mg vial	
		6 mg vial	
somapacitan (Sogroya)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults	5 mg/1.5 mL pen	6 mL/28 days
		10 mg/1.5 mL pen	
		15 mg/1.5 mL pen	

somatropin (Zomacton)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency • Small for gestational age • Turner syndrome	5 mg vial	Pediatric GHD: 0.3 mg/kg/week Adult GHD: 0.0875 mg/kg/week (0.0125 mg/kg/day) Idiopathic short stature: 0.37 mg/kg/week SHOX deficiency: 0.35 mg/kg/week Small for gestational age: 0.47 mg/kg/week Turner syndrome: 0.375 mg/kg week
		10 mg vial	
somatropin (Zorbtive)	Short bowel syndrome	8.8 mg vial	28 vials/28 days
Somatrogon-ghla (Ngenla)	Growth hormone deficiency (GHD), children	24mg/1.2mL pen	1.2mL/28days
		60mg/1.2mL pen	
lonapegsomatropin (Skytrofa)	Growth hormone deficiency (GHD), children	3.0 mg cartridge	4 cartridges/28 days
		3.6 mg cartridge	
		4.3 mg cartridge	
		5.2 mg cartridge	
		6.3 mg cartridge	
		7.6 mg cartridge	
		9.1 mg cartridge	
		11.0 mg cartridge	
		13.3 mg cartridge	

Growth Hormone Therapy in Children and Adolescents

Initial Evaluation

Genotropin and Omnitrope:
- There is no prior authorization required on these preferred agents unless requesting over the allowed quantity limits noted above.

I. **Somatropin (Humatrope, Norditropin, Nutropin AQ, Saizen, or Zomacton)** may be considered medically necessary for **children and adolescents** when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   B. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
   C. Member has not reached final height; **AND**
   D. A diagnosis of one of the following:

1. **Short stature associated with Turner Syndrome, Prader-Willi Syndrome, Noonan Syndrome, SHOX gene deficiency, or Chronic renal insufficiency; AND**
    i. The member has short stature as confirmed by one of the following:
        a. Current height: more than two standard deviations (SD) (less than 3rd percentile) below the mean for age and gender; **OR**
        b. Growth velocity: more than two SD below the mean for age and gender over one year; **OR**
        c. Growth velocity: more than 1.5 SD sustained over two years; **OR**
        d. Delayed skeletal maturation (delayed bone age): bone age compared to chronological age is equal to, or greater than, two SD below the mean for age and gender; **AND**
    ii. Treatment with Genotropin **AND** Omnitrope has been ineffective, contraindicated, or not tolerated if the request is for Turner syndrome or Prader-Willi Syndrome; **OR**
        a. Request is for Humatrope or Zomacton for SHOX gene deficiency; **OR**
        b. Request is for Nutropin AQ for chronic renal insufficiency; **OR**
        c. Request is for Norditropin in Noonan Syndrome; **OR**
        d. Request is for Norditropin in Prader-Willi Syndrome; **OR**
2. **Growth Hormone Deficiency; AND**
    i. Request is for Skytrofa; **AND**
        a. A trial with Genotropin **OR** Omnitrope of at least 12 months resulted in failure to achieve treatment goals for member growth due to lack of adherence; **OR**
        b. Member experienced intolerance, hypersensitivity, or has a contraindication to Genotropin and Omnitrope that is not expected to occur with Skytrofa; **OR**
    ii. Request is for somapacitan (Sogroya) or somatrogon-ghla (Ngenla); **AND**
        a. Treatment with Genotropin **OR** Omnitrope, followed by treatment with Skytrofa, has been ineffective, contraindicated, or not tolerated; **OR**
    iii. Request is for Humatrope, Norditropin, Nutropin AQ, Saizen, or Zomacton; AND
        a. Treatment with Genotropin **AND** Omnitrope has been ineffective, contraindicated, or not tolerated
3. **Growth failure in children born small for gestational age (SGA); AND**
    i. Member failed to manifest catch-up growth by two years of age; **AND**
    ii. Birth weight and/or length is less than two SD below the mean for gestational age; **AND**
    iii. Height remains less than two SD below the mean age and gender at two years of age; **AND**
    iv. Request is for Humatrope, Norditropin, or Zomacton; AND
        a. Treatment with Genotropin **AND** Omnitrope has been ineffective, contraindicated, or not tolerated.

Growth Hormone Therapy in Adults

Initial Evaluation

Genotropin and Omnitrope:

- There is no prior authorization required on these preferred agents, unless requesting over the allowed quantity limits noted above.

I. **Somatropin (Humatrope, Norditropin, Nutropin AQ, Saizen, or Zomacton) or somapacitan-beco (Sogroya)** may be considered medically necessary in **adults** when the following criteria below are met:

A. Medication is prescribed by, or in consultation with, an endocrinologist or gastroenterologist; **AND**

B. A diagnosis of one of the following:

1. **Short bowel syndrome; AND**
    i. Member is currently on specialized nutritional support that has been protein, calorie, and fluid intake-optimized for at least two weeks; **AND**
    ii. The request is for Zorbtive; **OR**
2. **HIV/AIDS associated wasting or cachexia; AND**
    i. Treatment with an appetite stimulant (dronabinol or megestrol) has been ineffective, contraindicated, or not tolerated; **AND**
    ii. The request is for Serostim; **OR**
3. **Adult Growth Hormone Deficiency (GHD); AND**
    i. Diagnosis of GHD that is one of the following:
        a. Adult onset from ONE of the following:
            i. genetic defects affecting the hypothalamic-pituitary axes;
            ii. hypothalamic-pituitary structural brain defects;
            iii. hypothalamic-pituitary disease with history of suprasellar mass with previous surgery and cranial radiation and evidence of multiple pituitary hormone deficiencies (≥3 pituitary hormone deficiencies [PHD]) and low-serum IGF-1 levels); **OR**
        b. Adult onset from ONE of the following:
            i. hypopituitarism due to pituitary disease;
            ii. traumatic brain injury;
            iii. hypothalamic-pituitary disease with history of suprasellar mass with previous surgery and cranial radiation and evidence of multiple pituitary hormone deficiencies (≤2 pituitary hormone deficiencies [PHD]) and low-serum IGF-1 levels; **AND**
                1. A subnormal response to any ONE of the following provocative growth hormone (GH) stimulation tests:
                    a. Clonidine
                    b. Glucagon
                    c. Insulin induced hypoglycemia

d. Propranolol; **OR**

c. Childhood-onset growth hormone deficiency; **AND**
   i. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range; **OR**

d. Idiopathic GH deficiency diagnosis; **AND**
   i. Diagnosis been confirmed by BOTH of the following:
      1. A subnormal response to any TWO of the following provocative growth hormone (GH) stimulation tests:
         a. Clonidine
         b. Glucagon
         c. Insulin induced hypoglycemia
         d. Propranolol; **AND**
      2. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range

ii. Treatment with Genotropin **AND** Omnitrope has been ineffective, contraindicated, or not tolerated.

II. Growth hormone is considered not medically necessary when used for all other conditions, including but not limited to:
   A. Idiopathic (i.e. of unknown origin) short stature, also called non-growth hormone deficient short stature in children
   B. Increased athletic performance in adults

III. Growth hormone is considered investigational when used for all other conditions, including but not limited to:
   A. Growth hormone insensitivity (Laron Syndrome)
   B. Constitutional growth delay
   C. Children with growth failure caused by glucocorticoids
   D. Children who are not growth hormone deficient but have short stature associated with chronic disease
   E. Children with chromosomal and genetic disorders (except Turner's and Prader Willi Syndromes) or familial short stature
   F. Russell Silver syndrome
   G. Altered body habitus or lipodystrophy associated with antiviral therapy
   H. Precocious puberty
   I. Obesity
   J. Cystic fibrosis
   K. Idiopathic dilated cardiomyopathy
   L. Juvenile idiopathic arthritis

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 through this health plan; **AND**
III. A diagnosis of one of the following:
    A. **Children with Growth Hormone Deficiency**
        a. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
        b. Member has not reached final height; **AND**
        c. Member has shown a response to growth hormone therapy (i.e., increase in height, increase in height velocity); **AND**
    B. **Children with short stature associated with Turner Syndrome, Prader-Willi Syndrome, Noonan Syndrome, SHOX Gene Deficiency, Chronic Renal Insufficiency, or Growth failure in children born small for gestational age (SGA); AND**
        a. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
        b. Member has not reached final height; **AND**
        c. Member has shown a response to growth hormone therapy (i.e. increase in height, increase in height velocity); **AND**
    C. **HIV/AIDS associated wasting or cachexia; AND**
        a. Member has shown clinical benefits by an increase in muscle mass and weight from growth hormone replacement; **AND**
        b. Member has not received more than six months of therapy; **OR**
    D. **Adult Growth Hormone Deficiency; AND**
        a. Member has shown clinical benefits from growth hormone replacement as assessed by one of the following:
            i. Normalization of insulin-like growth factor I (IGF-I)
            ii. Improvement in body composition (i.e. bone density increase, lipolysis changes)
            iii. Clinical assessment of patient focusing on improvement in quality of life issues

Supporting Evidence

I. All recombinant human growth hormone (GH) products that are administered via daily injections are somatropin, and other than device and FDA approved indications, there is little to no differentiation between these products. Skytrofa (lonapegsomatropin) and Ngenla (somatrogon-ghla) are long-acting, pegylated prodrug of a human growth hormone (somatropin) indicated in pediatric patients, offering once weekly dosing. Sogroya (somapacitan), provides the option of weekly administration in both adults and pediatrics; however, the adult efficacy results were based on a single trial in which numerical values compared to open-label Norditropin showed lower results in adults. Sogroya (somapacitan) was evaluated statistically only against placebo in a space with several established treatment options and patients in the trial were treatment naïve; thus, place in therapy and clinical efficacy compared to other available agents is unknown in adults.

II. Sogroya (somapacitan) was evaluated for children and adolescents in a Phase 3, randomized, multinational, open-label, active-controlled parallel group (somatropin [Norditropin®]) 52-week trial (REAL4) in 200 children and adolescents with treatment naïve growth hormone deficiency. The groups were randomized 2:1 in respect to weekly somapacitan (n=132) and daily somatropin (n=68).

III. Its primary outcome, longitudinal treatment difference in growth in children assessed by annualized height velocity (HV – cm/y), found weekly somapacitan (Sogroya) to be non-inferior to the active-controlled daily GH (somatropin [Norditropin®]). Secondary endpoints include change from baseline to week 52 in HV SD score (HD SDS), height SDS (HSDS), and bone age (BA) versus calculated age (CA) ratio.

IV. A two-year extension was completed where patients who received daily somatropin (Norditropin) were switched to receive weekly somapacitan (Sogroya) 0.16mg/kg/wk, while current weekly somapacitan patients were continued on therapy. Both groups (somapacitan group and the switch group) continued to show comparable efficacy in height velocity at week 104 versus the new "baseline" at week 52 in. Long-term safety was comparable to the original 52-week trial and there were no new safety signals in the extension. Overall quality of evidence in pediatrics is moderate as it is non-inferior to daily GH and the clinical outcomes measures are consistent with comparable treatment options.

V. The agents listed above with weight based dosing quantity limits also have an alternative dosing regimen available (0.2mg/day, increasing by 0.1 to 0.2mg/daily every 1 to 2 months according to response); however, this dosing would still be approvable as it would fall below the maximum weight based dose.

VI. The 2019 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) updated guidance to adult GHD discussed diagnostic parameters. They recommend that certain adult populations do not require GH stimulation testing to confirm diagnosis. That population includes patients with genetic defects that affect the hypothalamic-pituitary axes, hypothalamic-pituitary structural brain defects, and hypothalamic-pituitary disease with history of suprasellar mass with previous surgery and cranial radiation and evidence of multiple pituitary hormone deficiencies (≥3 pituitary hormone deficiencies [PHD]) and low-serum IGF-1 levels as these populations predict adult GHD with high specificity. The guidelines are silent on the number of confirmatory GH stimulation tests that should be completed on initial diagnosis.

VII. The diagnosis of GH deficiency is confirmed by measurement of GH secretion, commonly following stimulation by a provocative agent. The 2018 guideline update provides new guidance on growth hormone response thresholds based on the stimulation test.

- Insulin tolerance test (ITT) – less than 5 µg/L
- Glucagon-stimulation test
    i. Normal weight (BMI <25 mg/m^2) – 3 µg/L
    ii. Overweight with high pretest probability (BMI 25 to 30 kg/m^2) – 3 µg/L
    iii. Overweight with low pretest probability (BMI 25 to 30 kg/m^2) – 1 µg/L
    iv. Obese (BMI >30 kg/m^2) – 1 µg/L
- Macimorelin-stimulation test – 2.8 µg/L
- Arginine and levodopa testing is no longer recommended due to the low sensitivity/specificity in adults and lack of evidence and validation.

VIII. Due to a lack of evidence that one GH product is more beneficial than other, AACE does not recommend a particular product. AACE provides no guidance regarding length of GH therapy, but states that treatment should continue so long as benefits are seen. Discontinuation of GH treatment should be considered when no apparent benefits are achieved after at least two years of treatment.

IX. Somatropin and somapacitan should not be used for growth promotion in pediatric patients with closed epiphyses.

X. Zorbtive is indicated for the treatment of SBS in patients receiving specialized nutritional support. Administration for more than 4 weeks has not been adequately studied.

XI. Payment consideration for growth hormone used to treat HIV/AIDS wasting syndrome or cachexia is reserved for members that have had an inadequate response to appetite stimulants. Per package insert, there is no safety or efficacy data available from controlled studies in which patients were treated with Serostim continuously for more than 48 weeks. There is also no safety or efficacy data available from trials in which patients with HIV wasting or cachexia were treated intermittently with Serostim. A search in the medical literature as of September 2020 revealed two prospective controlled trials which are the pivotal trials in the Serostim package insert. The search did not identify any clinical studies or reports evaluating the use of human GH longer than 48 weeks in this treatment setting.

XII. Guidelines for Use of Growth Hormone in Clinical Practice: Patients with childhood-onset GH deficiency previously treated with GH replacement in childhood should be retested after final height is achieved and GH therapy discontinued for at least 1 month to ascertain their GH status before considering restarting GH therapy. Exceptions include those with known mutations, those with embryopathic/congenital defects, those with irreversible hypothalamic-pituitary structural lesions, and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off GH therapy.

- For childhood GH treatment of conditions other than GHD, such as Turner's syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved.

XIII. The Endocrine Society's clinical guidelines now recommend GH for use in idiopathic adult GH deficiency although this diagnosis is rare. Significant false-positive error rates occur in response to a single GH stimulation test; therefore, use of two tests is recommended before making a diagnosis. The 2019 guidelines do also recommend two tests, but only if the suspicion of idiopathic adult GHD is low. The presence of a low IGF-I also increases the likelihood that this diagnosis is correct.

FDA Approved Indications for Growth Hormone Products											
	GHD		TS	ISS	SGA	PWS	CKD	NS	SHOX	HIV	SBS
Brand	Ch	Ad									
Genotropin	x	x	x	x	x	x					
Humatrope	x	x	x	x	x				x		
Norditropin	x	x	x		x	x		x			
Nutropin AQ	x	x	x	x			x				
Omnitrope	x	x	x	x	x	x					

Saizen	x	x									
Zomacton	x	x	x	x	x				x		
Skytrofa	x										
Sogroya	x	x									
Ngenla	x										
Serostim										x	
Zorbtive											x

GHD = Growth Hormone Deficiency (Ch = Children, Ad = Adult)
TS = Turner Syndrome
ISS = Idiopathic Short Stature
SGA = Growth failure in children born Small for Gestational Age
PWS = Prader-Willi Syndrome in children
CKD = Growth failure due to chronic kidney disease
NS = Noonan Syndrome
SHOX = Short stature homeobox-containing gene deficiency
HIV = HIV-associated Wasting or Cachexia
SBS = Short Bowel Syndrome

Investigational or Not Medically Necessary Uses

I. Idiopathic short stature
   A. Growth hormone therapy for certain conditions may not be approved when use is not expected to correct a significant functional deficit or when reduced growth is not due to an underlying medical condition. Idiopathic short stature is a term used to define height of children who are short, for unknown or hereditary reasons, compared to others in their age- and gender appropriate reference range. Idiopathic short stature is not associated with a definable physical functional impairment, is not due to growth hormone deficiency, and is not the result of accidental injury, disease, trauma, or treatment of a disease, and is not a congenital defect. Additionally, the efficacy of growth hormone therapy for idiopathic short stature is highly variable and those that respond may only have modest additional growth. Growth hormone therapy may be prescribed to circumvent psychosocial burden associated with idiopathic short stature; however, treatment has not been proven effective in producing those intended effects on health outcomes, such as morbidity and quality of life. The potential for modest improvement in growth and unknown impact to psychosocial burden should be balanced with safety concerns associated with treatment including increased risk of cancer, cerebrovascular disease, and metabolic side effects. Given highly variable response rate, modest potential height gain, lack of underlying medical condition, unproven impact on psychosocial burden, and risk for adverse effects, treatment with growth hormone therapy is not medically necessary.

II. Increased athletic performance in adults
   A. The AACE recommends that GH should only be prescribed to patients with clinical features suggestive of adult GHD. Administration of GH to patients for improvement of athletic performance or for any reason other than its approved medical uses is not recommended.

III. There is insufficient or inconclusive medical and scientific evidence to support the safety and efficacy of growth hormone therapy in the listed conditions:
   A. Growth hormone insensitivity (Laron Syndrome)
   B. Constitutional growth delay

C. Children with growth failure caused by glucocorticoids
D. Children who are not growth hormone deficient but have short stature associated with chronic disease
E. Children with chromosomal and genetic disorders (except Turner's and Prader Willi Syndromes) or familial short stature
F. Russell Silver syndrome
G. Altered body habitus or lipodystrophy associated with antiviral therapy
H. Precocious puberty
I. Obesity
J. Cystic fibrosis
K. Idiopathic dilated cardiomyopathy
L. Juvenile idiopathic arthritis

References

1. Somatropin. Drug Facts & Comparisons [online; updated periodically]. Available from Wolters Kluwer Health, Inc.
2. Somatropin. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/
3. Omnitrope [Prescribing information]. Princeton, NJ: Sandoz Inc. February 2017.
4. Norditropin [Prescribing Information]. Bagsvaerd, Denmar: Novo Nordisk; Feb 2018.
5. Saizen [Prescribing Information]. Rockland, MA: EMD Serono Inc.; Dec 2016.
6. Serostim [Prescribing Information]. Rockland, MA: EMD Serono Inc.;Dec 2016.
7. Zorbtive[Prescribing Information]. Rockland, MA: EMD Serono Inc.; May 2017.
8. Humatrope [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC;Dec 2016.
9. Genotropin [Prescribing Information]. Belgium N.V., Puurs, Belgium: Pfizer Manufacturing; Dec 2016.
10. Zomacton [Prescribing Information]. Parsippany, NJ: Ferring Pharmaceuticals; Jan 2018.
11. American association of clinical endocrinologists Medical guidelines for clinical practice for Growth hormone use in growth hormone-deficient Adults and transition patients – 2009 update. Available at: https://www.aace.com/files/growth-hormone-guidelines.pdf.
12. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care – 2019 AACE Growth Hormone Task Force. Available at: https://www.endocrinepractice.org/action/showPdf?pii=S1530-891X%2820%2935145-4
13. Grimberg A, Divall SA, Polychronakos C, et al. Guidelines for Growth Hormone and Insulin-Like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-Like Growth Factor-I Deficiency. Horm Res Paediatr. 2016;86(6):361-397.
14. UpToDate, Inc. Diagnosis of growth hormone deficiency in children. UpToDate [database online]. Waltham, MA. Last updated Jan 06, 2018 Available at: http://www.uptodate.com/home/index.html.
15. Molitch ME, Clemmons DR, Malozowski S, Merriam GR, Vance ML. Evaluation and treatment of adult growth hormone deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(6):1587-609.
16. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab. 2000;85(11):3990-3.
17. Miller BS, Blair JC, Rasmussen MH, et al. Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial. J Clin Endocrinol Metab. 2022; 107(12):3378-3388.
18. Miller BS, Blair JC, Rasmussen MH, et al. Effective GH Replacement With Somapacitan in Children with GHD: REAL4 2-year Results and After Switch From Daily GH. J Clin Endocrinol Metab. 2023; 108(12):3090-3099.
19. Sogroya [Prescribing information]. Plainsboro, NJ: Novo Nordisk. October 2021. Updated April 2023.
20. Skytrofa [Prescribing information]. Palo Alto, CA: Ascendis Pharma, Inc. August 2021.
21. Ngenla [Prescribing information]. Pfizer. New York, NY. June 2023.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updates to improve clarity of intent regarding previous treatment requirements. Replaced Skytrofa step of Omnitrope/Genotropin failure description from a growth velocity of at least 2 cm/year to instead failure to achieve treatment goals for growth.	05/2024
Addition of new indication for pediatric growth hormone deficiency for Sogroya and related supportive evidence. Updated criteria for adult growth hormone deficiency based on AACE/ACE 2019 guidelines and supportive evidence. Addition of Omnitrope as a preferred agent.	03/2024
Addition of somatrogon (Ngenla) to non-preferred position.	11/2023
Requirement of trial of lonapegsomatropin (Skytrofa) and Genotropin in pediatric growth hormone deficiency setting. Removal of confirmatory diagnostic criteria in setting of pediatric growth hormone deficiency setting. Update to not medically necessary supporting evidence for idiopathic short stature.	07/2022
Addition of new product lonapegsomatropin in non-preferred position	08/2021
Addition of new product Sogroya in non-preferred position	02/2021
Created separate policy documents for consortium and non-consortium commercial groups. For non-consortium group, updated to Genotropin exclusive preferred product.	01/2021
Added further supporting evidence to duration of therapy with Serostim in the setting of HIV/AIDS associated wasting or cachexia. Updated to Omnitrope exclusive preferred product.	11/2020
Updated to policy format. Updated growth hormone stimulation requirements to align with guideline recommendations (Molitch 2011 and Grimberg 2016). Added requirement of treatment to be prescribed by specialist. Removed route for coverage in the setting of idiopathic short stature as growth hormone therapy for certain conditions may not be approved when growth hormone use is not expected to correct a significant functional deficit OR when reduced growth is not due to an underlying medical condition.	11/2019
Criteria update: updated criteria to new format, deleted question defining HIV wasting, added routing questions for growth failure in children born small for gestational age added clinical notes to questions.	03/2018
Criteria Created	08/2014