Oxbryta (voxelotor)

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indication

Oxbryta is indicated for the treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older. This indication is approved under accelerated approval based on increase in hemoglobin (Hb). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

There are no data available to support the use of Oxbryta (voxelotor) in combination with Adakveo (crizanlizumab-tmca).

POLICY

Required Documentation

Submission of the following information is necessary to initiate the prior authorization review:

A. Initial therapy requests
   1. Documentation of baseline hemoglobin. Note: Requirements regarding pretreatment hemoglobin level exclude values due to a recent transfusion.
   2. Documentation of treatment failure, intolerance or contraindication to hydroxyurea if not currently receiving hydroxyurea
   3. Documentation supporting the clinical reason why the member should avoid Adakveo

4. Documentation supporting the need to adjust dosing to the higher dose of 2,500 mg per day to account for a drug interaction with a strong or moderate CYP3A4 inducer and why coadministration is unavoidable.

B. Continuation of therapy requests
   1. Documentation of an increase in hemoglobin levels since baseline or a maintained increase in hemoglobin, since initiating therapy with Oxbryta.
   2. Documentation of treatment failure, intolerance or contraindication to hydroxyurea if not currently receiving hydroxyurea

Criteria for Initial Approval

A. Oxbryta (voxelotor) may be considered **medically necessary** for the treatment of sickle cell disease when the following criteria are met:
   1. The member is 4 years of age and less than 16 years of age; OR the member is 16 years and older and has a clinical reason to avoid Adakveo
   2. The member has a diagnosis of sickle cell disease of any genotype, including, but not limited to, homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle beta^0 thalassemia, and sickle beta$^+$ thalassemia
   3. Oxbryta is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of sickle cell disease
   4. The member has previously experienced 1 or more sickle cell-related vasoocclusive crises within the previous 12 months
   5. Baseline hemoglobin range is ≥ 5.5 g/dL and ≤ 10.5 g/dL.
   6. The member is currently receiving and will continue to receive hydroxyurea in conjunction with Oxbryta; OR the member has a documented history of treatment failure, intolerance or contraindication to hydroxyurea
   7. Oxbryta will not be used in conjunction with Adakveo (crizanlizumab-tmca)
   8. If requesting tablets for oral solution, member must demonstrate a medical reason they are unable to utilize oral tablets (e.g., age, dysphagia, oral/motor difficulties, administered through feeding tube)
   9. Dose does not exceed 1,500 mg (3 tablets) per day
      OR
      The dosing will be adjusted to 2,500 mg (5 tablets) per day due to the patient taking a strong or moderate CYP3A4 inducer and documentation supports that coadministration is unavoidable

Approval will be for **6 months**

Continuation of Therapy

A. Oxbryta (voxelotor) may be considered **medically necessary** for the continued treatment of sickle cell disease when the following criteria are met:
   1. The member has a diagnosis of a sickle cell disease, including, but not limited to, homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], sickle beta^0 thalassemia, and sickle beta$^+$ thalassemia
   2. Oxbryta is prescribed by, or in consultation with, a hematologist, or other specialist with expertise in the diagnosis and management of sickle cell disease
   3. The member has experienced a positive clinical benefit to Oxbryta therapy as evidenced by a documented increase in hemoglobin levels since baseline of at least 1 g/dL, or has maintained such increase, since initiating therapy with Oxbryta.
   4. The member is currently receiving hydroxyurea; OR the member has a documented history of treatment failure, intolerance or contraindication to hydroxyurea
   5. Oxbryta will not be used in conjunction with Adakveo (crizanlizumab-tmca)

Approval will be for **12 months**

Dosage and Administration
Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits
Standard Limit: 3 tablets/day
Exception Limit: 5 tablets/day

CLINICAL RATIONALE

Sickle cell disease (SCD) is an autosomal recessive genetic disorder characterized by the presence of hemoglobin S (HbS) (i.e., sickle hemoglobin), which results from substitution of the amino acid valine for glutamic acid at the sixth position of the beta globin chain. This mutation causes red blood cells (RBCs) to develop a sickled (i.e., crescent) shape, which leads to clinical signs and symptoms. The hallmarks of SCD are hemolytic anemia and recurrent pain episodes (i.e., sickle cell-related pain crises or vasoocclusive crises [VOCs]), and patients may experience organ dysfunction and premature death.

Oxbryta (voxelotor) is a HbS polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization. Nonclinical studies suggest that voxelotor may inhibit RBC sickling, improve RBC deformability, and reduce whole blood viscosity.

Efficacy
The efficacy of Oxbryta (voxelotor) was evaluated in the HOPE trial, a Phase III, randomized, double-blind, placebo-controlled study in 274 patients with SCD. Patients received 1500 mg of voxelotor, 900 mg of voxelotor, or placebo. Enrolled patients had from 1 to 10 VOCs within the 12 months prior to enrollment and a baseline hemoglobin level ≥ 5.5 to ≤ 10.5 g/dL. Sixty-five percent of patients were on stable doses of hydroxyurea for at least 90 days prior to enrollment and were allowed to continue therapy during the trial.
Overall, 83.9% (230 out of 274) of patients completed the study through week 24. The primary endpoint was the percentage of patients who had a hemoglobin response, which was defined as an increase of more than 1.0 g/dL in hemoglobin from baseline at week 24. After 24 weeks of treatment, 51% of patients receiving 1500 mg voxelotor had a hemoglobin response compared to 7% in the placebo group ($p < 0.001$). In the 900 mg voxelotor group, 33% of patients had a hemoglobin response at week 24 ($p < 0.001$ vs. placebo). The percentages of patients who underwent RBC transfusions during the trial period were similar in the 3 trial groups (33% in the voxelotor 1500 mg group, 32% in the voxelotor 900 mg group and 25% in the placebo group). Most transfusions were performed because of acute VOCs.

As a secondary endpoint, the study also evaluated the annualized incidence rate of VOCs (per person-year); the rate was 2.77 with voxelotor 1500 mg and 2.76 with voxelotor 900 mg vs. 3.19 with placebo. The percentages of participants who had at least 1 VOC were 67% in the voxelotor 1500 mg group, 66% in the voxelotor 900 mg group and 69% in the placebo group. Other secondary endpoints included the change in hemoglobin, percent change in indirect bilirubin, and percent reticulocyte count from baseline to week 24. In the voxelotor 1500 mg group, the mean changes from baseline to week 24 for hemoglobin, indirect bilirubin, and percent reticulocyte were 1.1 g/dL, -29.1%, and -19.9%, respectively. In the placebo group, the mean changes from baseline to week 24 for hemoglobin, indirect bilirubin, and percent reticulocyte were -0.1 g/dL, -3.2%, and 4.5%, respectively.

Long-term follow-up studies are planned to evaluate the effect of the increase in hemoglobin level and decrease in hemolysis induced by voxelotor on morbidity and mortality among persons with sickle cell disease.

Safety
Hypersensitivity reactions (i.e., rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia) have occurred in <1% of patients treated with Oxbryta. Oxbryta (voxelotor) should not be reinitiated in patients who experienced hypersensitivity reactions with previous use. The most common adverse events reported in Oxbryta (voxelotor) and placebo patients were headache (26% vs. 22%),

diarrhea (20% vs. 10%), abdominal pain (19% vs. 13%), nausea (17% vs. 10%), fatigue (14% vs. 10%), rash (14% vs. 10%) and pyrexia or fever (12% vs. 7%). The rate of grade 3 or higher adverse events and the rate of discontinuation were similar among the groups. In addition, there is a lack of long-term safety data with use of Oxbryta (voxelotor), which is concerning since its mechanism by which it improves anemia is by increasing hemoglobin oxygen affinity. This may adversely impact tissue oxygen delivery; however, no significant safety signals were highlighted in the pivotal trial.

Co-administration of Oxbryta (voxelotor) and a strong cytochrome P450 (CYP) 3A4 inhibitor or fluconazole should be avoided as the combination may increase voxelotor plasma concentrations and lead to toxicity. The dose of Oxbryta (voxelotor) should be decreased if use with a strong CYP3A4 inhibitor or fluconazole cannot be avoided. Co-administration of Oxbryta (voxelotor) with a strong or moderate CYP3A4 inducer may decrease Oxbryta (voxelotor) concentrations and may lead to reduced efficacy. This combination should also be avoided, or the dose of Oxbryta (voxelotor) should be increased if concomitant use cannot be avoided. Co-administration of Oxbryta with sensitive CYP3A4 substrates with a narrow therapeutic index should be avoided, or the dose of the CYP3A4 substrate should be reduced. Oxbryta (voxelotor) may also interfere with high-performance liquid chromatography (HPLC) measurement of Hb subtypes (i.e., HbA, HbS, and HbF).

In summary, Oxbryta (voxelotor) may provide benefit to Sickle Cell Disease patients who are inadequately managed by other treatment options and can be used in combination with hydroxyurea, however, data establishing a clinical benefit is lacking. In clinical trials, Oxbryta demonstrated a 1 g/dL increase in hemoglobin levels and reduced markers of hemolysis vs placebo but data have not shown a reduction in red blood cell transfusions or vasoocclusive crises (VOCs). While that degree of improvement in hemoglobin was associated with significantly decreased rates of multiorgan failure and death in natural history studies and is considered a response to therapy with Oxbryta, further trials are needed to verify clinical benefit and its impact on morbidity and mortality. Due to the lack of evidence demonstrating a clinical benefit and the fact that Adakveo (crizanlizumab-tmca) did demonstrate a lower annual rate of vasoocclusive crises (VOCs) in clinical trials, the criteria for approval of Oxbryta will be limited to those patients who are not able to receive Adakveo (i.e. patients 12-15 years of age or patients 16 years and older who have a clinical reason to avoid Adakveo).

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- N/A

REFERENCES

- Oxbryta [package insert]. South San Francisco, CA: Global Blood Therapeutics, Inc.; December 2021
- Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. N Engl J Med. 2019 Aug 8;381(6):509-519.
- Han J, Saraf SL, & Gordeuk VR. Systematic Review of Voxelotor: A First-in-Class Sickle Hemoglobin Polymerization Inhibitor for Management of Sickle Cell Disease. *Pharmacotherapy*. 2020;40(6):525-534.

*Some content reprinted from CVSHealth

POLICY HISTORY

Policy #: 05.04.04
Policy Creation: April 2020

Reviewed: October 2022
Revised: February 2021
Current Effective Date: April 4, 2022