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## **Subject: Voxelotor (Oxbryta™)**

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

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### **DESCRIPTION:**

Sickle cell disease (SCD) represents a group of inherited disorders carried by the beta allele of the hemoglobin (Hb) gene. It is characterized by abnormal hemoglobin polymerization that results in a sickle-shaped erythrocyte. This sickled alteration results in a shortened lifespan of the erythrocyte (16 days vs 120 days in normal RBCs) and ultimately results in vascular occlusion.

The term SCD includes the homozygous genotype HbSS and the heterozygous genotypes HbS $\beta^0$  thalassemia, HbSC, HbSD, and HbS $\beta^+$  thalassemia. An individual with one normal gene and one HbS gene (HbAS) is a carrier and referred to as “sickle cell trait”. Sickle cell trait typically does not have clinical manifestations of the disease.

Acutely, patients with SCD present with recurrent pain episodes, life-threatening infections due to splenic infarction, acute chest syndrome, pulmonary hypertension, stroke, and cumulative multiorgan damage. These episodes are categorized as vaso-occlusive crises (VOCs). Treatment options for SCD predominantly focus on management of symptoms and secondary complications and include hydroxyurea, L-glutamine, and blood transfusions. The only curative option is hematopoietic cell transplantation.

Voxelotor was approved by the U.S. Food and Drug Administration (FDA) in December 2019 for the treatment of the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older. This indication was approved under accelerated approval based on increase in hemoglobin. Continued approval for this indication may be contingent upon verification and description of clinical

benefit in confirmatory trial. In December 2021, this label was expanded to include pediatric patients 4-12 years old.

Voxelotor works by inhibiting hemoglobin S (HbS) polymerization. Consequently, this improves RBS deformity, inhibits RBC sickling, and reduces whole blood viscosity.

The safety and efficacy of voxelotor were evaluated in a phase III, placebo-controlled trial (HOPE trial). Individuals with SCD were randomized to receive a once-daily oral dose of 1500 mg of voxelotor (n=90) or placebo (n=92). The trial included a screening period of 28-35 days, a treatment period up to 72 weeks, and an end-of-trial visit 3-5 weeks subsequent to the last dose of the trial regimen.

Patients 12-65 years of age were eligible to participate in the HOPE trial if they had any genotype of SCD, a hemoglobin level between 5.5 and 10.5 g per deciliter (g/dL) during screening, and experienced 1-10 SCD-related acute pain crises in the 12 months prior to enrollment. Patients who had been receiving hydroxyurea at a stable dose for at least 3 months prior to enrollment were permitted to continue therapy during the trial. Patients were excluded if they were receiving chronic red-cell transfusions, had received a transfusion in the past 60 days, or had been hospitalized for an SCD-related acute pain crisis within 14 days of providing informed consent.

Patients in the voxelotor group had a median age of 24 years and were made up of 64% females; 66% of the trial population were black, 68% had an HbSS SCD genotype, and 64% were receiving concomitant therapy with hydroxyurea. The proportions of patients with 1 versus 2-10 SCD-related crises in the previous year, was 39% and 61%, respectively.

The primary endpoint was the proportion of patients who had a hemoglobin response, defined as an increase from baseline in hemoglobin of more than 1.0 g/dL at week 24. The annualized rate of SCD-related acute pain crises was evaluated as a secondary endpoint. SCD-related acute pain crises was defined as a composite of ACS and/or moderate to severe pain lasting at least 2 hours with no explanation other than a vaso-occlusive event. The crises must have required oral or parenteral opioids, ketorolac, or other analgesics and have been documented in a medical record that the patient was seen or contacted a physician within 1 business day of the event.

Compared to optimal usual care alone (i.e., placebo), voxelotor increased hemoglobin levels and reduced markers of hemolysis. It did not significantly reduce the number of acute pain crises and did not improve quality of life as measured by the study. At week 24, 51% of the voxelotor group and 7% of the placebo group ( $p<0.001$ ) had a response. Improvements in hemoglobin were observed as early as 2 weeks of follow-up. At week 24, the adjusted mean change in hemoglobin from baseline was 1.1 g/dL (95% CI 0.9 to 1.4) in the voxelotor group and -0.1 g/dL (95% CI -0.3 to 0.2;  $p<0.001$ ).

The annualized incidence rate of SCD-related acute pain crisis was evaluated as a secondary endpoint in the HOPE trial and did not differ among trial arms. In the voxelotor group, there were 2.77 (95% CI 2.15 to 3.57) crises per person-year versus 3.19 (95% CI 2.50 to 4.07) in the placebo group (incidence rate ratio 0.87 [95% CI 0.61 to 1.23]); 67% and 69% of patients in the voxelotor and placebo arms, respectively, had at least 1 crisis. Investigators noted that a longer duration of follow-up is required to evaluate the effect of voxelotor on the incidence of acute pain crises. A final analysis will be performed when all subjects complete 72 weeks of treatment or their final study visit.

Sickle cell anemia with crisis, ACS, pneumonia, priapism, and osteonecrosis were recorded as SCD-related TEAEs in the HOPE trial. Collectively, these events occurred in 76% of voxelotor-treated patients and 73% of placebo-treated patients. Rates of SAEs and treatment discontinuation due to an AE were relatively low in the HOPE trial of voxelotor. The most commonly reported AEs were diarrhea, nausea, abdominal pain, rash, and headache.

The Institute for Clinical and Economic Review (ICER) will release a final evidence report in April 2020 to assess the comparative clinical effectiveness and value of treatments in sickle cell disease.

## **POSITION STATEMENT:**

### **Comparative Effectiveness**

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of voxelotor (Oxbryta) **meets the definition of medical necessity** when all of the following criteria are met:

1. Indication for use is sickle cell disease (SCD) – documentation from the medical record must be provided
2. Member has experienced at least one sickle cell-related pain crisis in the past 12 months or member is 4 years to less than 12 years of age – documentation from the medical record must be provided
3. Member has a baseline hemoglobin of less than 10.5 g/dL – documentation from the medical record must be provided
4. Member meets one of the following:
  - a. Member is currently receiving a hydroxyurea product
  - b. Member has a history of treatment failure, intolerance, or contraindication to hydroxyurea therapy
5. Use will not be in combination with crizanlizumab-tcma (Adakveo)
6. Treatment is prescribed by or in consultation with a board certified (or board eligible) hematologist
7. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for SCD
8. Dose does not exceed 1500 mg daily with the following exception:
  - a. Concomitant use with strong or moderate CYP3A4 inducers: 2,500 mg once daily

**Approval duration:** 6 months

Continuation of voxelotor (Oxbryta) **meets the definition of medical necessity** when all of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years for treatment of sickle cell disease (SCD), **OR** the member has previously met all indication-specific initiation criteria
2. Member has demonstrated a beneficial response to treatment with voxelotor as evidenced by one of the following – documentation from medical record must be provided
  - a. Increase from baseline in hemoglobin of more than 1.0 g/dL
  - b. Reduction from baseline in sickle cell-related pain crises
3. Use will not be in combination with crizanlizumab-tcma (Adakveo)
4. Treatment is prescribed by or in consultation with a board certified (or board eligible) hematologist
5. Member is not concurrently enrolled in a clinical trial to receive an experimental therapy for SCD
6. Dose does not exceed 1500 mg daily with the following exception:
  - a. Concomitant use with strong or moderate CYP3A4 inducers: 2,500 mg once daily

**Approval duration:** 6 months

## **DOSAGE/ADMINISTRATION:**

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

### **FDA-approved**

- Adults and pediatric patients 12 years and older: 1,500 mg orally once daily with or without food
- Pediatric patients 4 years to less than 12 years:
  - 40 kg or greater: 1,500 mg daily
  - 20 kg to less than 40 kg: 900 mg daily
  - 10 kg to less than 20 kg: 600 mg daily

### **Dose Adjustments**

- Severe hepatic impairment: 1,000 mg orally once daily in patients with severe hepatic impairment (Child Pugh C)
- Concomitant use with strong CYP3A4 inhibitors or fluconazole: 1,000 mg once daily
- Concomitant use with strong or moderate CYP3A4 inducers: 2,500 mg once daily

### **Drug Availability**

- Tablets 500 mg
- Tablets for oral suspension: 300 mg

## PRECAUTIONS:

### Boxed Warning

- None

### Contraindications

- Prior drug hypersensitivity to voxelotor or excipients

### Precautions/Warnings

- Hypersensitivity Reactions: Observe for signs and symptoms and manage promptly
- Laboratory Test Interference: Perform quantification of hemoglobin species when patient is not receiving

## BILLING/CODING INFORMATION:

The following codes may be used to describe:

### HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified
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### ICD-10 Diagnosis Codes That Support Medical Necessity

D57.00	Hb-SS disease with crisis unspecified
D57.01	Hb-SS disease with acute chest syndrome
D57.02	Hb-SS disease with splenic sequestration
D57.04	Hb-SS disease with dactylitis
D57.21	Sickle cell/Hb-C disease with crisis
D57.211	Sickle cell/Hb-C disease with acute chest syndrome
D57.212	Sickle cell/Hb-C disease with splenic sequestration
D57.214	Sickle-cell/Hb-C disease with dactylitis
D57.219	Sickle cell/Hb-C disease with crisis, unspecified
D57.41	Sickle cell thalassemia with crisis
D57.411	Sickle cell thalassemia with acute chest syndrome
D57.412	Sickle cell thalassemia with splenic sequestration
D57.414	Sickle-cell thalassemia, unspecified, with dactylitis
D57.419	Sickle cell thalassemia with crisis, unspecified
D57.434	Sickle-cell thalassemia beta zero with dactylitis
D57.454	Sickle-cell thalassemia beta plus with dactylitis
D57.81	Other sickle cell disorders with crisis
D57.811	Other sickle cell disorders with acute chest syndrome
D57.812	Other sickle cell disorders with splenic sequestration
D57.814	Other sickle-cell disorders with dactylitis
D57.819	Other sickle cell disorders with crisis unspecified

## REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

## DEFINITIONS:

**Acute Hepatic Sequestration:** patients with hepatic sequestration usually present with right upper quadrant pain, rapidly increasing hepatomegaly, and a falling hematocrit.

**Acute Kidney Injury/Renal Infarction:** a condition resulting from a sudden disruption of blood flow to the renal artery. This may cause irreversible damage to kidney tissues.

**Chronic Kidney Disease (Nephropathy):** defined in trials as either having a glomerular filtration rate (GFR) of less than 60ml/min/1.73 m<sup>2</sup> for greater than or equal to 3 months with or without kidney damage or having evidence of kidney damage for greater than or equal to 3 months, with or without decreased GFR, manifested by either pathologic abnormalities or markers of kidney damage independent of cause.

**Chronic Sickle Cell Pain:** pain that does not resolve and lasts for more than 3 months.

**HbS $\beta$ 0 thalassemia** occurs in patients who inherit one sickle cell gene and one beta thalassemia gene that results in no production of HbA.

**HbS $\beta$ + thalassemia** occurs in patients who inherit one sickle cell gene and one beta thalassemia gene resulting in reduced production of HbA.

**HbSC:** sickle cell hemoglobin C disease

**HbSD, HbSE and HbSO22:** one inherited sickle cell gene ("S") and one gene from an abnormal type of hemoglobin ("D", "E" or "O").

## RELATED GUIDELINES:

None

## OTHER:

None

## REFERENCES:

1. Brown C, Hoppe C, Inati A, et al. Efficacy and Safety of 1500 mg Voxelotor in a Phase 2a Study (GBT440-007) in Adolescents with Sickle Cell Disease. *Blood*:132(Suppl 1):509.
2. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2024 [cited 4/1/24]. Available from: <http://www.clinicalpharmacology.com/>.
3. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 4/1/24]. Available from: <http://clinicaltrials.gov/>.
4. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 4/1/24].
5. Global Blood Therapeutics. Oxbryta (voxelotor) tablet. 2022 [cited 4/1/22]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3c557fac-29ec-483f-b691-8a935d4decc3/>.
6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 4/1/24]. Available from: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/>.

## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/14/25.

## GUIDELINE UPDATE INFORMATION:

03/15/20	New Medical Coverage Guideline.
07/15/21	Review and revision to guidelines; updated position statement and references.
05/15/22	Review and revision to guidelines; updated description, dosage/administration, coding, and references.
07/15/22	Revision to guideline; updated position statement.
10/01/23	Revision to guideline; ICD10 code update.
05/15/24	Review and revision to guidelines; updated position statement and references.
01/15/26	MCG Archived