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Oxbryta Prior Authorization with Quantity Limit Program Summary

FDA APPROVED INDICATIONS AND DOSAGE[1]

Agent(s)	Indication(s)	Dosage
Oxbryta® (voxelotor) Oral tablets Tablet for oral suspension	• Treatment of sickle cell disease in adults and pediatric patients 12 years of age and older	**Sickle cell disease:** 1500 mg orally once daily

CLINICAL RATIONALE

Sickle cell disease (SCD) is the name given to a group of lifelong inherited conditions that affect hemoglobin. People with SCD have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle or crescent shape.[2]

Signs and symptoms of SCD usually begin in early childhood. Characteristic features of SCD include anemia, repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person and can range from mild to requiring frequent hospitalizations.[2]

SCD effects nearly every system in the body resulting in both acute and chronic complications. An episode of severe pain [acute vaso-occlusive crisis (VOC)] is the most common acute complication of SCD. In addition to VOCs other common acute complications of SCD include fever related to infection, acute kidney injury (AKI), hepatobiliary complications, acute anemia, splenic sequestration, acute chest syndrome (ACS), and acute stroke. Certain acute complications often evolve into chronic phases. The most common chronic complications of SCD include chronic pain, chronic anemia, avascular necrosis, leg ulcers, pulmonary hypertension, renal complications, stuttering/recurrent priapism, and ophthalmologic complications.[2]

Pain is the most common complication of SCD. People with SCD experience both nociceptive and neuropathic pain. Pain can be acute, chronic, or an acute episode superimposed on chronic pain. In SCD, pain is considered chronic if it lasts more than 3 months.[2]

Recurrent and unpredictable episodes of vaso-occlusion are the hallmark of sickle cell disease. Discoveries over the past 2 decades have highlighted the important contributions of various cellular and soluble participants in the vaso-occlusive cascade. Although the molecular basis of SCD is well characterized, the complex mechanisms underlying VOC have not been fully elucidated. Based on direct observations in SCD mice, adhesive interactions of SS-RBCs and leukocytes to the endothelium play important roles in the initiation of VOC. It is thought that the activated adherent leukocytes, which are rigid and larger than sickle cell-red blood cells (SS-RBC), likely drive VOC in collecting venules, whereas the SS-RBCs may contribute in smaller vessels or in situations where there is no potent inflammatory trigger.[4]

Triggers for VOC vary and can include inflammation, stress, increased viscosity, decreased flow, hemolysis, or a combination of the following factors:[4]

- Endothelial activation by SS-RBCs and other inflammatory mediators

- Recruitment of adherent leukocytes
- Activation of recruited neutrophils and of other leukocytes (e.g., monocytes or iNKT cells)
- Interactions of sickle erythrocytes with adherent neutrophils
- Vascular clogging by heterotypic cell-cell aggregates composed of SS-RBCs, adherent leukocytes and possibly platelets
- Increased transit time to greater than the delay time for deoxygenation-induced hemoglobin polymerization, propagating retrograde VOC
- Ischemia as a result of the obstruction that creates a feedback loop of worsening endothelial activation

Sickle hemoglobin can cause damage to the RBC membrane from deformation by polymer formation. In addition, the mutated globin can undergo autooxidation and precipitate on the inner surface of the RBC membrane, causing membrane damage via iron-mediated generation of oxidants. Both endothelial selectins, P-selectin and E-selectin, have been suggested to participate in VOC.[4]

Nearly all people with SCD have chronic anemia, but individual baseline hemoglobin values vary widely depending upon hemoglobin genotype (HbSS, HbSC, HbSβ^+-thalassemia, HbSβ^0-thalassemia). It is important for the patient and the primary care provider to know the baseline or "steady state" hemoglobin value for ongoing monitoring and management during acute complications.[2]

Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as an option to increase hemoglobin-F (HbF) levels in people with SCD. The initial clinical trial of hydroxyurea for the treatment of sickle cell anemia (SCA) involved two people. The results of this study showed favorable outcomes which lead to two extended studies with larger cohorts of people. Although HbF induction is the most powerful effect of hydroxyurea and provides the biggest direct benefit for people who have SCD, additional mechanisms of actions and benefits exist. Hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters the expression of adhesion molecules, all of which contribute to vaso-occlusion. Hydroxyurea also raises RBC volume [higher mean corpuscular volume (MCV)] and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion.[3]

An expert panel report of evidence-based management of sickle cell disease supports the use of hydroxyurea with strong recommendations in the following:[3]
- In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12 month period
- In adults with SCA who have sickle cell-associated pain that interferes with daily activity and quality of life
- In adults with SCA who have a history of severe and/or recurrent acute coronary syndrome (ACS)
- In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life
- In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia)

A clinical response to treatment with hydroxyurea may take 3-6 months. Therefore, the expert panel recommends a 6 month trial on the maximum tolerated dose prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.[3]

Efficacy[1]
Oxbryta (voxelotor) is a hemoglobin S (HbS) polymerization inhibitor that binds HbS with a 1:1 stoichiometry and exhibits preferential partitioning to red blood cells (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.

The efficacy and safety of Oxbryta in sickle cell disease was evaluated in HOPE, a randomized, double blind, placebo-controlled, multicenter trial involving 274 patients. Eligible patients on stable doses of hydroxyurea for at least 90 days could continue hydroxyurea therapy throughout the study. Patients were included if they had from 1 to 10 vaso-occlusive crisis events with 12 months prior to enrollment and baseline hemoglobin ≥ 5.5 and ≤ 10.5 g/dL. The trial excluded patients who received red blood cell transfusions within 60 days and erythropoietin within 28 days of enrollment, had renal insufficiency, uncontrolled liver disease, were pregnant, or lactating.

Efficacy of the HOPE trial was based on Hb response rate defined as a Hb increase of > 1 g/dL from baseline to week 24 in patients treated with Oxbryta vs placebo. The response rate for Oxbryta 1,500 mg was 51% compared to 6.5% in the placebo group (p<0.001).

Additional efficacy evaluation included change in Hb and percent change in indirect bilirubin and percent reticulocyte count from baseline to week 24. The results are shown in the table below.

	Oxbryta 1,500 mg daily (N=90)	**Placebo (N=92)**	**P Value**
Hemoglobin	1.14 g/dL (0.13)	-0.08 g/dL (0.13)	<0.001
Indirect bilirubin	-29.08% (3.48)	-3.16 (3.52)	<0.001
Percent reticulocyte count	19.93% (4.60)	4.54% (4.60)	<0.001

Safety[1]
- **Oxbryta** (voxelotor) is contraindicated in prior drug hypersensitivity to voxelotor or excipients

References

1. Oxbryta Prescribing Information. Global Blood Therapeutics, Inc. December 2021.
2. U.S. National Library of Medicine. Genetics Home Reference. Sickle cell disease. November 2019.
3. U.S. Department of Health and Human Services. National Institute of Health. Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014.
4. Manwani D, Frenette PS, Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Blood. 2013 Dec 5; 122(24): 3892-3898.

Oxbryta (voxelotor) Prior Authorization with Quantity Limit

TARGET AGENT(S)
Oxbryta® (voxelotor)

Brand (generic)	GPI	Multisource Code	Quantity Limit (per day or as indicated)
Oxbryta (voxelotor)			
300 mg tablet for oral suspension	82805080007320	M, N, O, or Y	5 tablets
500 mg tablets	82805080000320	M, N, O, or Y	3 tablets

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of sickle cell disease
   AND
2. ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent
      OR
   B. The prescriber has provided information in support of using the requested agent for the patient's age
   AND
3. ONE of the following
   A. The patient has tried and had an inadequate response to maximally tolerated hydroxyurea for at least 6 months
      OR
   B. The patient has an intolerance or hypersensitivity to hydroxyurea
      OR
   C. The patient has an FDA labeled contraindication to hydroxyurea
   AND
4. ONE of the following:
   A. The patient's baseline (pretreatment) hemoglobin is ≥ 5.5 and ≤ 10.5 g/dL
      OR
   B. The patient's baseline (pretreatment) hemoglobin is below the lab reference range for the patient's age and gender
   AND
5. ONE of the following:
   A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Endari (L-glutamine)
      OR
   B. Information has been provided supporting the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Endari (L-glutamine)
   AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
7. ONE of the following:
   A. The requested quantity (dose) does NOT exceed the program quantity limit
      OR
   B. ALL of the following:

i. The requested quantity (dose) is greater than the program quantity limit
AND
ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
AND
iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 6 months

Renewal Evaluation
Target Agent(s) will be approved when ALL of the following are met:
1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process
AND
2. The patient has had clinical benefit with the requested agent indicated by one of the following:
    A. The patient had an increase in hemoglobin level of greater than 1 g/dL from baseline
    OR
    B. The patient has a hemoglobin level within the normal range for age and gender
    OR
    C. Information has been provided supporting continuation with the requested agent (medical records required)
AND
3. ONE of the following:
    A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Endari (L-glutamine)
    OR
    B. Information supporting the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Endari (L-glutamine)
AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent
AND
5. ONE of the following:
    A. The requested quantity (dose) does NOT exceed the program quantity limit
    OR
    B. ALL of the following:
        i. The requested quantity (dose) is greater than the program quantity limit
        AND
        ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication
        AND
        iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: 12 months