Oxbryta (voxelotor) Prior Authorization with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
12-01-2024

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Oxbryta® (voxelotor) Oral tablets Tablet for oral suspension	Treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older		1

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Sickle cell disease	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 affects 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 sickle cell-red blood cells (SS-RBC) 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 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 fetal hemoglobin (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) While hydroxyurea remains the first-line therapy for SCD, L-glutamine, crizanlizumab, and voxelotor have been approved as adjunctive or second-line treatments, and hematopoietic stem cell transplant with a matched sibling donor is now standard care for severe disease. The emergence of gene therapies for SCD now bring the potential for curative therapy without a matched donor.(5)
Efficacy	Oxbryta (voxelotor) is a hemoglobin S (HbS) polymerization inhibitor that binds HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. By increasing the affinity of hemoglobin (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.(1) 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 greater than or equal to 5.5 and less than or equal to 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.(1) Efficacy of the HOPE trial was based on Hb response rate defined as a Hb increase of greater than 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 ($p < 0.001$).(1) Additional efficacy evaluation included change in Hb and percent change in indirect bilirubin and percent reticulocyte count from baseline to week 24. The results for Hb were 1.1 g/dL with Oxbryta 1,500 mg daily vs -0.1 g/dL with placebo. For indirect bilirubin, results were -29.1% with Oxbryta 1,500 mg daily vs -2.8% with placebo. For Percent reticulocyte count the results were -18% for Oxbryta 1,500 mg daily vs 6.8% with placebo.(1)b response rate, which is defined as a Hb increase of greater than 1 g/dL from baseline to Week 24. Hb response rate for Oxbryta in patients aged 4 to less than 12 years who took at least one dose of Oxbryta was 36% (95% CI).(1) Hb response rate, which is defined as a Hb increase of greater than 1 g/dL from baseline to Week 24. Hb response rate for Oxbryta in patients aged 4 to less than 12 years who took at least one dose of Oxbryta was 36% (95% CI).(1) The efficacy and safety of Oxbryta in patients 4 to less than 12 years with sickle cell disease was evaluated in an open-label, multi-center, Phase 2 trial (NCT 02850406). Patients were included if their baseline Hb was less than or equal to 10.5 g/dL. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. The trial excluded patients who had a VOC event within 14 days prior to enrollment, received RBC transfusions within 30 days of enrollment, and had renal insufficiency or uncontrolled liver disease.(1) Efficacy was based on Hb response rate, which is defined as a Hb increase of greater than 1 g/dL from baseline to Week 24. Hb response rate for Oxbryta in patients aged 4 to less than 12 years who took at least one dose of Oxbryta was 36% (95% CI).(1)
Safety	Oxbryta (voxelotor) is contraindicated in patients with a history of serious drug hypersensitivity reaction drug hypersensitivity to voxelotor or excipients.(1)

REFERENCES

Number	Reference
1	Oxbryta Prescribing Information. Global Blood Therapeutics, Inc. August 2023.
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.
5	Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. Journal of Hematology & Oncology. 2022;15(1). doi:10.1186/s13045-022-01237-z.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Oxbryta	voxelotor tab ; voxelotor tab for oral susp	300 MG ; 500 MG	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Oxbryta	Voxelotor Tab	300 MG	90	Tablets	30	DAYS			
Oxbryta	Voxelotor Tab 500 MG	500 MG	90	Tablets	30	DAYS			
Oxbryta	Voxelotor Tab For Oral Susp	300 MG	90	Tablets	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Oxbryta	voxelotor tab ; voxelotor tab for oral susp	300 MG ; 500 MG	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Oxbryta	Voxelotor Tab	300 MG	Commercial ; HIM ; ResultsRx
Oxbryta	Voxelotor Tab 500 MG	500 MG	Commercial ; HIM ; ResultsRx
Oxbryta	Voxelotor Tab For Oral Susp	300 MG	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical 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. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following A. The patient has tried and had an inadequate response after at least 6 months duration of therapy with maximally tolerated hydroxyurea **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 (before treatment with the requested agent) hemoglobin is greater than or equal to 5.5 g/dL and less than or equal to 10.5 g/dL **OR** B. The patient's baseline (before treatment with the requested agent) 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) for the requested indication **OR** B. There is support for the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Endari (L-glutamine) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria **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 [Note: patients not previously approved for the requested agent will require initial evaluation review] **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 (before treatment with the requested agent) **OR** B. The patient has a hemoglobin level within the normal range for age and gender **OR** C. There is support for 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) for the requested indication **OR** B. There is support for the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Endari (L-glutamine) for the requested indication **AND**

Module	Clinical Criteria for Approval
	4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND BOTH of the following: A. ONE of the following: 1. The requested agent is Oxbryta 500 mg tablets **OR** 2. The requested agent is Oxbryta 300 mg tablets AND there is support for why the patient cannot take 3 tablets of Oxbryta 500 mg strength **AND** B. ALL of the following: 1. BOTH of the following: A. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** B. There is support for therapy with a higher dose for the requested indication **OR** 2. BOTH of the following: A. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** B. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. BOTH of the following: A. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** B. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months