BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 2/13/2020**
SECTION: DRUGS	**LAST REVIEW DATE: 2/17/2022**
	LAST CRITERIA REVISION DATE: 2/17/2022
	ARCHIVE DATE:

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Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Oxbryta (voxelotor) with or without generic hydroxyurea is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Hematologist or Pediatric Hematologist
  2. Individual is 12 years of age or older
  3. A confirmed diagnosis of sickle cell disease in an individual who has had at least one vaso-occlusive crisis (VOC) event within the last 12 months
  4. Hemoglobin is between 5.5-10.5 g/dL
  5. Individual has failure, (at least 3 months), contraindication per FDA label, or intolerance to generic monotherapy hydroxyurea
  6. Individual is not receiving concomitant chronic, prophylactic blood transfusion therapy or has not received red blood cell transfusions within the last 60 days
  7. Individual has not received erythropoiesis stimulating agent (i.e., Aranesp (darbepoetin), Epogen (epoetin alpha, etc.) within the last 28 days
  8. Individual does not have end stage renal disease requiring dialysis
  9. Individual will not be receiving Adakveo (crizanlizumab) or Endari (l-glutamine) concurrently
  10. There are no significant interacting drugs

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Oxbryta (voxelotor) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Hematologist or Pediatric Hematologist
  2. Individual's condition responded while on therapy
     a. Response is defined as:
        i. No evidence of disease progression
        ii. Documented evidence of efficacy (at least an increase in hemoglobin of > 1 g/dL), disease stability and/or improvement
  3. Individual has been adherent with the medication

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4. Individual has not developed any significant adverse drug effects that may exclude continued use
5. Individual is not receiving concomitant chronic, prophylactic blood transfusion therapy or has not received red blood cell transfusions within the last 60 days
6. Individual has not received erythropoiesis stimulating agent (i.e., Aranesp (darbepoetin), Epogen (epoetin alpha, etc.) within the last 28 days
7. Individual does not have end stage renal disease requiring dialysis
8. Individual will not be receiving Adakveo (crizanlizumab) or Endari (l-glutamine) concurrently
9. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:
  1. **Off-Label Use of Non-cancer Medications**
  2. **Off-Label Use of Cancer Medications**

Description:

Oxbryta (voxelotor) is indicated for the treatment of sickle cell disease (SCD) in adults and pediatric patients 12 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 trial(s).

Oxbryta (voxelotor) is a hemoglobin S (HbS) polymerization inhibitor that reversibly binds to Hb and stabilizes the oxygenated Hb state. Through the increased Hb affinity for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization, and may inhibit RBC sickling, improve RBC deformability, and reduce whole blood viscosity. Voxelotor may also extend RBC half-life and reduce anemia and hemolysis.

SCD is caused by a single amino acid substitution on the β–globin resulting in the production of sickle hemoglobin (HbS). HbS polymerizes when deoxygenated, resulting in red-cell sickling and membrane damage. These abnormalities lead to hemolysis, chronic anemia, inflammation, and vaso-occlusion, which cause the acute and chronic manifestations of sickle cell disease.

Homozygous hemoglobin SS (HbSS) (i.e., sickle cell anemia [SCA]) and HbSβ^0-thalassemia are the most common SCD genotypes; they are clinically similar and are associated with the most severe clinical manifestations

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Deoxygenated sickle hemoglobin (HbS) polymerization drives the pathophysiology of sickle cell disease. Inhibiting HbS polymerization in red cells could have a disease-modifying effect. Because the rate of HbS polymerization is extremely sensitive to deoxygenated HbS concentration, small changes in concentration can have substantial effects on polymerization. This hypothesis is supported by the absence of symptoms of sickle cell disease in persons who are compound heterozygotes for HbS and deletional hereditary persistence of fetal hemoglobin, who have anti-sickling fetal hemoglobin levels of approximately 30%.

Current treatment includes symptom improvement for acute veno-occlusive crises (VOCs) (e.g., pain management, intravenous hydration, and oxygen), antibiotic prophylaxis, increasing hemoglobin levels long term through RBC transfusions, and strategies to decrease the number of VOCs. Oral therapy includes hydroxyurea and l-glutamine have demonstrated effectiveness in reducing the number of VOCs and are currently used in treatment.

The only proven disease-modifying therapies for SCD are hydroxyurea and chronic blood transfusions. Both therapies are used in primary and secondary stroke prevention. Currently there are no comprehensive, systematically reviewed, evidence-based guidelines for the management of SCD.
However, the National Institutes of Health (NIH) sponsored, evidence-based expert consensus guidelines was published in 2014. Per NIH consensus treatment guidelines, hydroxyurea is considered the standard of care for both adults with painful SCCs and other chronic complications, and for pediatric patients regardless of clinical severity, to reduce SCD-related complications.

Hydroxyurea has resulted significantly fewer SCD-related event seen are reductions in the incidence of pain, acute chest syndrome (ACS), rate of dactylitis, and fewer hospitalizations. Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5 to 10 mg/kg/day if patient has chronic kidney disease. Starting dosage for infants and children: 20 mg/kg/day. A clinical response to treatment with hydroxyurea may take 3 to 6 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.

Hydroxyurea is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with SCA with recurrent moderate to severe painful crises. Hydroxyurea is available as Droxia (for patients 18 years of age or older), Siklos (for patients 2 years of age or older), and as a generic formulation (used off-label in patients 18 years of age or older). L-glutamine is indicated to reduce the acute complications of SCD in adult and pediatric patients ≥ 5 years of age.

Voxelotor is a first-in-class HbS polymerization inhibitor is now available for patients ≥ 12 years of age and older.

Definitions:

Vaso-occlusive crises (VOC):
A composite of acute painful crisis or acute chest syndrome (ACS) and the following:

- Moderate to severe pain lasting ≥ 2 hours
- No explanation other than VOC
- Requires oral or parental opioids, ketorolac, or other analgesics prescribed or directed by a healthcare professional

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- Must be documented in medical record that the patient was seen or contacted a physician within 1 business day of the event. The event may take place in a medical setting (e.g., hospital, clinic, emergency room)
- May include episodes of ACS (ACS is defined as an acute illness characterized by fever and/or respiratory symptoms, accompanied by a new pulmonary infiltrate on a chest Xray)

Therapies for Sickle Cell Disease	
Hydroxyurea: Droxia 200 mg, 300 mg, 400 mg caps	Droxia is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises
Siklos 100 mg, 1,000 mg tabs	Siklos is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients, 2 years of age and older, with sickle cell anemia with recurrent moderate to severe painful crises
Hydrea & generics 500 mg cap (Off- label)	Adult: 15 mg/kg/day (round up to the nearest 500 mg) Infant: 20 mg/kg/day
Endari (L-glutamine) 5 gram oral powder	Endari is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older
Oxbryta (voxelotor) 500 mg tab	Oxbryta is indicated for the treatment of sickle cell disease (SCD) in adults and pediatric patients 12 years of age and older
Adakveo (crizanlizumab-tmca) 100 mg/10 mL	Adakveo is indicated to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease

National Institutes of Health (NIH). National Heart, Lung, and Blood Institute (NHLBI). Evidence-based management of SCD. Expert Panel Report, 2014

- The only proven disease-modifying therapies for SCD are hydroxyurea and chronic blood transfusions.
- Although neither has been shown to prevent all SCD-related organ damage, these treatment modalities can improve the QOL for individuals with SCD.
- Recommendations for hydroxyurea therapy:
  - Adults with SCA who have ≥ 3 sickle cell-associated moderate to severe pain crises in a 12-month period should be treated with hydroxyurea.
  - Adults with SCA who have sickle cell-associated pain that interferes with daily activities and QOL should be treated with hydroxyurea.
  - Adults with SCA who have a history of severe or recurrent ACS should be treated with hydroxyurea.
  - Adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or QOL should be treated with hydroxyurea.
  - For infants ≥ 9 months of age, children, and adolescents with SCA, treatment with hydroxyurea should be offered regardless of clinical severity to reduce SCD-related complications (eg, pain, dactylitis, ACS, anemia).
  - A clinical response to hydroxyurea may take 3-6 months; therefore, a 6-month trial on the maximum tolerated dose is required prior to discontinuation due to treatment failure, whether due to lack of adherence or failure to respond.

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- For patients with a clinical response to hydroxyurea, long-term hydroxyurea therapy is indicated.
- In people not demonstrating a clinical response to appropriate doses and duration of hydroxyurea therapy, a sickle cell expert should be consulted

Multicenter Study of Hydroxyurea (MSH) in Patients with Sickle Cell Anemia	
Charache et al NEJM 1995; 332 (20):1317-1322 (MSH pivotal trial)	• Patients in the hydroxyurea group (n = 152) had lower annual rates of sickle cell crises (SCCs) compared with patients in the placebo group (n = 147) (median, 2.5 vs 4.5 crises per year; p < 0.001). • The median annual rates of SCCs requiring hospitalization were 1.0 vs 2.4 per year, respectively; p < 0.001. • The median times to first VOC (3.0 vs 1.5 months; p = 0.01) and second VOC (8.8 vs 4.6 months; p < 0.001) were longer with hydroxyurea treatment. • The incidence of death, stroke, and hepatic sequestration were not significantly different between groups. However, fewer patients receiving hydroxyurea developed ACS (25 vs 51 in the placebo group; p < 0.001) and fewer received blood transfusions (48 vs 73; p = 0.001).
Steinberg et al JAMA 2003; 289 (13):1645-1651 (MSH 9 year follow-up)	• Follow-up data for up to 9 years were complete for 233 (77.9%) of the 299 enrolled patients. • In the MSH patients' follow-up, patients could continue, stop, or start hydroxyurea. Ninety-six (32%) patients never received hydroxyurea; 48 (16%) received hydroxyurea for < 1 year; and 156 (53%) received hydroxyurea for ≥ 1 year. • 75 of the original 299 patients (25.1%) died, 28% from pulmonary disease. • **Patients with ≥ 3 SCCs per year during the trial had 27% mortality compared with 17% of patients with less frequent episodes (p = 0.06).**
Steinberg et al Am J Hematol 2010; 85 (6):403-408 (MSH 17.5 year follow-up)	• Follow-up data for up to 17 years and 7 months were complete for all 299 patients enrolled in the initial trial. • **Mortality was reduced in individuals with long-term exposure to hydroxyurea; of the 129 out of 299 patients who died, and 87.1% occurred in patients who never took hydroxyurea or took it for < 5 years.** • **Stroke, organ dysfunction, infection, and malignancy were similar in all groups.**

Resources:

Oxbryta (voxelotor) tab product information, revised by Global Blood Therapeutics, Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 21, 2021.

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Field JJ, Vichinsky EP. Overview of the management and prognosis of sickle cell disease. In: UpToDate, DeBaun MR, Timauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated December 09, 2020. Accessed December 23, 2021.

Vichinsky EP. Disease-modifying therapies to prevent pain and other complications of sickle cell disease. In: UpToDate, DeBaun MR, Timauer JS (Eds), UpToDate, Waltham MA.: UpToDate Inc. http://uptodate.com. Topic last updated October 21, 2021. Accessed December 23, 2021.

Bradt P, Spackman E, Synnott PG, Chapman R, Beinfeld M, Rind DM, Pearson SD. Crizanlizumab, Voxelotor, and L-Glutamine for Sickle Cell Disease: Effectiveness and Value. Institute for Clinical and Economic Review, January 23, 2020. https://icer-review.org/material/sickle-cell-disease-draft-evidence-report/ Accessed January 15, 2021. Re-reviewed December 23, 2021.

Gibbons GH, Shurin SB, Buchanan GR, Yawn BP, et al.: National Institutes of Health (NIH). National Heart, Lung, and Blood Institute (NHLBI). Evidence-based management of SCD. Expert Panel Report, 2014. Accessed February 11, 2020. Re-reviewed January 15, 2021. Re-reviewed December 23, 2021.