

Pharmacy Management Drug Policy

SUBJECT: Sickle Cell Disease Management

POLICY NUMBER: PHARMACY-84

EFFECTIVE DATE: 12/2019

LAST REVIEW DATE: 06/24/2024

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	<input checked="" type="checkbox"/> Commercial Group (e.g., EPO, HMO, POS, PPO)	<input checked="" type="checkbox"/> Medicare Advantage
	<input checked="" type="checkbox"/> On Exchange Qualified Health Plans (QHP)	<input type="checkbox"/> Medicare Part D
	<input checked="" type="checkbox"/> Off Exchange Direct Pay	<input checked="" type="checkbox"/> Essential Plan (EP)
	<input checked="" type="checkbox"/> Medicaid & Health and Recovery Plans (MMC/HARP)	<input checked="" type="checkbox"/> Child Health Plus (CHP)
	<input type="checkbox"/> Federal Employee Program (FEP)	<input type="checkbox"/> Ancillary Services
	<input checked="" type="checkbox"/> Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Sickle Cell Disease (SCD) represents a group of genetic disorders characterized by structural abnormalities in hemoglobin (Hb). A single amino acid substitution is responsible for the production of sickle hemoglobin (HbS). There are several variant genotypes of the normal adult hemoglobin (Hb AA) that cause SCD, with the most prevalent including HbSS, HbSC, HbS/β+ thalassemia, and HbS/β0 thalassemia.¹ SCD affects millions worldwide, including an estimated 100,000 Americans.²

The primary event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS. Polymerization alters cellular morphology, creating red blood cells (RBCs) that are rigid and 'sickle-shaped.'³ These damaged RBCs have a substantially shorter lifespan and disrupt normal blood and oxygen flow to parts of the body. Complications of SCD include vaso-occlusive crisis (VOCs), hemolytic anemia, acute chest syndrome, stroke, pulmonary hypertension, deep vein thrombosis, infection, and splenic sequestration.^{2,4} VOCs are one of the main reasons for healthcare encounters.

Adakveo® (Crizanlizumab-tmca) is a monoclonal antibody that targets P-selectin, a cellular adhesion molecule found in vascular endothelial cells and platelets. Binding P-selectin blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes, reducing frequency of VOCs.⁵

Endari™ (L-glutamine) is an amino acid precursor of pyridine nucleotides. These nucleotides contribute to the regulation and prevention of oxidative damage to RBCs. Sickle RBCs are more susceptible to oxidative stress. Oxidative phenomena are involved in the pathophysiology of SCD.⁶

Oxbryta™ (Voxelotor) binds to HbS, increasing affinity for oxygen and inhibits HbS polymerization. Studies suggest this may inhibit sickling, improve deformability, and decrease whole blood viscosity.⁷

Siklos® (Hydroxyurea) is an antimetabolite with an unknown precise mechanism in SCD. Benefits include increasing hemoglobin F levels in RBCs, decreasing neutrophils, increasing water content of RBCs, increasing deformability of sickled cells, and altering adhesion of RBCs to the endothelium.⁸

Pharmacy Management Drug Policy

Sickle Cell Disease Management

POLICY:

Based upon our assessment and review of the peer-reviewed literature Adakveo, Endari, Oxbryta and Siklos have been medically proven to be effective and therefore, **medically necessary** for the treatment of Sickle Cell disease if specific criteria are met:

Adakveo - Crizanlizumab-tmca (Medical)

1. Must have a diagnosis of Sickle cell disease (SCD) **AND**
2. Must be prescribed by, or in consultation with, a Hematologist or provider who specializes in management of SCD **AND**
3. Member must be at least 16 years of age **AND**
4. Must have documentation of ≥ 1 vaso-occlusive crisis (VOCs) event(s) within the preceding 12 months that required a medical facility visit (ER, clinic, hospital, local physician visit) **AND**
 - a. Examples of VOC events include but are not limited to: acute episode of pain caused by VOC, acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism.
5. Must have had (See **Table 1** for additional hydroxyurea info) (**either a or b**):
 - a. A therapeutic failure (ex. continued frequent and/or severe VOCs or ongoing, frequent transfusion requirements) to a ≥ 6 -month trial of hydroxyurea at max tolerated dosing **OR**
 - b. Must have experienced **two** hematologic toxicity reactions with hydroxyurea that resulted in discontinuation of therapy.
 - i. Hematologic toxicity with hydroxyurea is defined by neutrophil, platelet, hemoglobin and/or reticulocyte count abnormalities concurrent with hydroxyurea use suggestive of hematologic toxicity. After the first hematologic toxicity, hydroxyurea therapy should be stopped and can be restarted with a dose reduction upon hematologic recovery. If a second hematologic toxicity is experienced, treatment should be discontinued.
6. Adakveo will not be approved in combination with Oxbryta or Endari as there are currently no clinical studies evaluating the combinations **AND**
7. Approval will be for 6 months. Recertifications will be for 1 year and require documentation of a decrease in the number and/or severity (ex. fewer/shorter hospitalizations) of VOCs compared to baseline.

FDA-approved dosing: 5mg/kg IV infusion over 30 minutes at Weeks 0, 2, and every 4 weeks thereafter.

Pharmacy Management Drug Policy

Sickle Cell Disease Management

Endari – L-glutamine oral powder (Rx)

1. Must have a diagnosis of Sickle Cell Disease type HbSS or HbS/β0 thalassemia as determined by hemoglobin electrophoresis **AND**
2. Member must be at least 5 years old **AND**
3. Must be experiencing symptomatic pain that is a result of Sickle Cell Disease **AND**
4. Must have had (See **Table 1** for additional hydroxyurea info) (**either a or b**):
 - a. A therapeutic failure (ex. continued frequent and/or severe VOCs or ongoing, frequent transfusion requirements) to a ≥ 6-month trial of hydroxyurea at max tolerated dosing **OR**
 - b. Must have experienced **two** hematologic toxicity reactions with hydroxyurea that resulted in discontinuation of therapy
 - i. Hematologic toxicity with hydroxyurea is defined by neutrophil, platelet, hemoglobin and/or reticulocyte count abnormalities concurrent with hydroxyurea use suggestive of hematologic toxicity. After the first hematologic toxicity, hydroxyurea therapy should be stopped and can be restarted with a dose reduction upon hematologic recovery. If a second hematologic toxicity is experienced, treatment should be discontinued.
5. Quantity limit exceptions will require a recent (within the past 6 months) weight and will be approved in accordance with the FDA-approved weight-based dosing as follows:
 - a. 30-65kg = 120 packets/30 days
 - b. >65kg = 180 packets/30 days
6. Endari will not be approved in combination with Oxbryta or Adakveo as there are currently no clinical studies evaluating the combinations **AND**
7. Approval will be for one year. Recertification will require documentation of improvement in Sickle Cell Disease related pain.

Oxbryta 300 mg Tablets, 500mg Tablets and 300mg Tablets for Oral Suspension – Voxelotor (Rx)

1. Must have a diagnosis of Sickle cell disease (SCD) **AND**
2. Must be prescribed by, or in consultation with, a Hematologist or provider who specializes in management of SCD **AND**
3. Member must be at least 4 years of age **AND**
4. Baseline hemoglobin (measured within 60 days) must be:
 - a. ≥12 years of age: ≥5.5 to ≤10.5 g/dL
 - b. 4 years to less than 12: ≤10.5 g/dL **AND**
5. For members ≥12 years of age only, must have documentation of ≥1 vaso-occlusive crisis (VOCs) event(s) within the preceding 12 months that required a medical facility visit (ER, clinic, hospital, local physician visit) **AND**
 - a. Examples of VOC events include but are not limited to acute episode of pain caused by VOC, acute chest syndrome, hepatic sequestration, splenic sequestration, or priapism.
6. Must have had (See **Table 1** for additional hydroxyurea info) (**either a or b**):
 - a. A therapeutic failure (ex. continued frequent and/or severe VOCs or ongoing, frequent transfusion requirements) to a ≥ 6-month trial of hydroxyurea at max tolerated dosing **OR**
 - b. Must have experienced **two** hematologic toxicity reactions with hydroxyurea that resulted in discontinuation of therapy
 - i. Hematologic toxicity with hydroxyurea is defined by neutrophil, platelet, hemoglobin and/or reticulocyte count abnormalities concurrent with hydroxyurea use suggestive of hematologic toxicity. After the first hematologic toxicity, hydroxyurea therapy should be stopped and can be restarted with a dose reduction upon hematologic recovery. If a second hematologic toxicity is experienced, treatment should be discontinued. **AND**

Pharmacy Management Drug Policy

Sickle Cell Disease Management

7. Use of **300 mg tablets for oral suspension** will require documentation of a swallowing disorder (a swallowing evaluation must be submitted to confirm) for:
 - a. Individuals \geq 12 years **OR**
 - b. ANY individual that requires a daily dose of 1,500 mg or more **AND**
8. Use of **300 mg tablets** will not be approved for ANY member that requires a daily dose of 1,500 mg or more and will require use of the 500 mg tablet.
 - a. Individuals 4 years to < 12 years that weigh 40 kg or more and taking Oxbritya with a concomitant:
 - i. Moderate CYP3A4 inducer must utilize the 500 mg tablets to obtain a daily dose of 2,000 mg (four 500 mg tablets) **OR**
 - ii. Strong CYP3A4 Inducer must utilize the 500 mg tablets to obtain a daily dose 2,500 mg (five 500 mg tablets)
9. Oxbritya will not be approved for use in combination with Adakveo or Endari as there are currently no clinical studies evaluating the combinations **AND**
10. Approval will be for 6 months. Recertification will be for 1 year and require a \geq 1 g/dL increase in hemoglobin compared to baseline (measured within 60 days). Subsequent yearly recertifications will require documentation of hemoglobin levels maintained \geq 1 g/dL compared to baseline.
11. Quantity limit: 90 tablets/30 days (for all strengths and dosage forms)
 - a. Individuals 4 years to < 12 years of age weighing 20 kg to < 40 kg and taking Oxbritya with a concomitant moderate CYP3A4 inducer may obtain a quantity limit exception of 120 tablets/30 days (1,200 mg/day) for the 300 mg tablets or 300 mg tablets for oral suspension.

Siklos – hydroxyurea tablets (Rx)

1. Must have a diagnosis of Sickle cell disease (SCD) **AND**
 2. Must be 2 years of age or older **AND**
 3. If the requested dose is exactly divisible by available strengths of Hydroxyurea or Droxia, the patient will be required to use those unless there is a valid medical reason, they are unable. If not divisible, proceed to Steps 4 **AND** 5
 - a. Hydroxyurea: 500mg capsules
 - b. Droxia: 200mg, 300mg, 400mg capsules
 - c. Siklos: 1000mg (can split into quarters for doses of 250, 500, 750 or 1000mg; also available as 100mg (can split in half for doses of 50mg)
 4. Step therapy applies - Must have experienced a hematologic toxicity reaction with the next highest dose that can be made by using Droxia or generic hydroxyurea capsules **AND**
 - a. Hematologic toxicity with hydroxyurea is defined by neutrophil, platelet, hemoglobin and/or reticulocyte count abnormalities concurrent with hydroxyurea use suggestive of hematologic toxicity. After the first hematologic toxicity, hydroxyurea therapy should be stopped and can be restarted with a dose reduction upon hematologic recovery.
 5. Step therapy applies - Must have had drug failure (ex. continued frequent and/or severe VOCs or ongoing, frequent transfusion requirements) with the next lowest dose that can be made by using Droxia or generic hydroxyurea capsules
- Example 1: Prescriber requests Siklos 700mg per day (1000mg x1/2 + 100mg x2), the patient would be required to use Droxia (300mg x1 + 400mg x1).
- Example 2: If a prescriber requests Siklos 750 mg per day (3/4 tab), the patient would be required to have a hematologic toxicity reaction with two Droxia 400 mg capsules taken together to make 800 mg per day **AND** drug failure with two Droxia 300 mg capsules taken together to make 600 mg per day

Pharmacy Management Drug Policy

Sickle Cell Disease Management

POLICY GUIDELINES:

1. Unless otherwise stated above within the individual drug criteria, approval time-period will be for 2 years.
 - a. Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary. Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e., generics, biosimilars, or other guideline-supported treatment options). Requested dosing must continue to be consistent with FDA-approved or off-label/guideline-supported dosing recommendations.
2. Utilization Management are contract dependent and coverage criteria may be dependent on the contract renewal date. Additionally, coverage of drugs listed in this policy are contract dependent. Refer to specific contract/benefit language for exclusions.
3. For contracts where Insurance Law § 4903(c-1), and Public Health Law § 4903(3-a) are applicable, if trial of preferred drug(s) is the only criterion that is not met for a given condition, and the requesting prescriber provides rationale and documentation for one of the following circumstances, then trial of the preferred drug(s) will not be required.
 - a. The required prescription drug(s) is (are) contraindicated or will likely cause an adverse reaction or physical or mental harm to the member
 - b. The required prescription drug is expected to be ineffective based on the known clinical history and conditions and concurrent drug regimen
 - c. The required prescription drug(s) was (were) previously tried while under the current or a previous health plan, or another prescription drug or drugs in the same pharmacologic class or with the same mechanism of action was (were) previously tried and such prescription drug(s) was (were) discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event
 - d. The required prescription drug(s) is (are) not in the patient's best interest because it will likely cause a significant barrier to adherence to or compliance with the plan of care, will likely worsen a comorbid condition, or will likely decrease the ability to achieve or maintain reasonable functional ability in performing daily activities
 - e. The individual is stable on the requested prescription drug. The medical profile of the individual (age, disease state, comorbidities), along with the rationale for deeming stability as it relates to standard medical practice and evidence-based practice protocols for the disease state will be taken into consideration.

The above criteria are not applicable to requests for brand name medications that have an AB rated generic. We can require a trial of an AB-rated generic equivalent prior to providing coverage for the equivalent brand name prescription drug.

4. This policy is applicable to drugs that are included on a specific drug formulary. If a drug referenced in this policy is non-formulary, please reference the Non-Formulary Medication Exception Review Policy for review guidelines.
5. Not all contracts cover all Medical Infusible drugs. Refer to specific contract/benefit plan language for exclusions of Injectable Medications.
6. This policy does not apply to Medicare Part D and D-SNP pharmacy benefits. The drugs in this policy may apply to all other lines of business including Medicare Advantage.
7. For members with Medicare Advantage, medications with a National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) will be covered pursuant to the criteria outlined by the

Pharmacy Management Drug Policy

Sickle Cell Disease Management

NCD and/or LCD. NCDs/LCDs for applicable medications can be found on the CMS website at <https://www.cms.gov/medicare-coverage-database/search.aspx>. Indications that have not been addressed by the applicable medication's LCD/NCD will be covered in accordance with criteria determined by the Health Plan (which may include review per the Health Plan's Off-Label Use of FDA Approved Drugs policy). Step therapy requirements may be imposed in addition to LCD/NCD requirements.

8. This policy is subject to frequent revisions as new medications come onto the market. Some drugs will require prior authorization prior to criteria being added to the policy.
9. Supportive documentation of previous drug use must be submitted for any criteria that require a trial of a preferred agent if the preferred drug is not found in claims history.
10. Dose and frequency should be in accordance with the FDA label or recognized compendia (for off-label uses). When services are performed in excess of established parameters, they may be subject to review for medical necessity.
11. Adakveo is administered by IV infusion and is covered under the medical benefit.
12. Siklos, Endari, and Oxbryta are orally administered and are covered under the pharmacy benefit.
13. Table 1: NIH Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy¹

Initiation

- Starting dosage for adults (500 mg capsules): 15 mg/kg/day (round up to the nearest 500 mg); 5–10 mg/kg/day if patient has chronic kidney disease
- Starting dosage for infants and children: 20 mg/kg/day

Monitor

- Monitor CBC with WBC differential and reticulocyte count at least every 4 weeks when adjusting dosage.
- Aim for target ANC =2,000/uL; however, younger patients with lower baseline counts may safely tolerate absolute neutrophil counts down to 1,250/uL.
- Maintain platelet count =80,000/uL

Management of toxicities

- If neutropenia or thrombocytopenia occurs:
 - Hold hydroxyurea dosing
 - Monitor CBC with WBC differential weekly
 - When blood counts have recovered, reinstitute hydroxyurea at a dose 5 mg/kg/day lower than the dose given before onset of cytopenias

Response considerations

- A clinical response to treatment with hydroxyurea may take *3–6 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.
- A lack of increase in MCV and/or HbF is *not* an indication to discontinue therapy.

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.

Codes may not be covered under all circumstances. Please read the policy and guidelines statements carefully.

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Pharmacy Management Drug Policy

Sickle Cell Disease Management

Code Key:

Experimental/Investigational = (E/I),

Not medically necessary/ appropriate = (NMN).

Copyright © 2006 American Medical Association, Chicago, IL

HCPCS: J0791: Adakveo

UPDATES:

Date	Revision
06/24/2024	Revised
04/11/2024	Revised
02/08/2024	Reviewed / P&T Committee Approval
12/06/2023	Revised
8/16/2023	Revised
3/15/2023	Revised
2/9/2023	P&T Committee Approval
2/14/2022	Revised
2/10/2022	Reviewed / P&T Committee Approval
2/3/2022	Revised
1/12/2022	Revised
2/11/2021	P&T Committee Approval
1/21/2021	Revised
8/28/2020	Revised
6/8/2020	Revised
4/12/2020	Revised
2/21/2020	Revised
2/13/2020	P&T Committee Approval
12/16/2019	Created

REFERENCES:

1. The National Institutes of Health – National Heart, Lung, and Blood Institute Evidence-Based Management of Sickle Cell Disease, Expert Panel Report 2014. Available at: <http://www.nhlbi.nih.gov/guidelines>. Accessed on December 8th, 2019
2. Centers for Disease Control and Prevention. Sickle Cell Disease. <https://www.cdc.gov/ncbddd/sicklecell/index.html>. Accessed December 8th, 2019.
3. Vichinsky E, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *N Engl J Med*. 2019;381(6):509-519.
4. Ataga KI, et al. Crizanlizumab for the Prevention of Pain Crisis in Sickle Cell Disease. *N Engl J Med*. 2017;376(5):429-439.
5. Adakveo® injection for intravenous use [prescribing information]. East Hanover, NJ: Novartis; November 2019.
6. Endari™ oral powder [prescribing information]. Torrance CA: Emmaus Medical, Inc; July 2017
7. Oxbryta™ tablets [prescribing information]. South San Francisco CA: Global Blood Therapeutics, Inc; December 2021.
8. Siklos® tablets [prescribing information]. Bryn Mawr, PA: Medunik USA Inc; May 2018.