# Pharmacy Management Drug Policy

**SUBJECT: Sickle Cell Disease Management**
**POLICY NUMBER: PHARMACY-84**
**EFFECTIVE DATE: 12/2019**
**LAST REVIEW DATE: 03/05/2026**

*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**

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|---|---|---|
| **Category**: | ☒ Commercial Group (e.g., EPO, HMO, POS, PPO) | ☒ Medicare Advantage |
| | ☒ On Exchange Qualified Health Plans (QHP) | ☐ Medicare Part D |
| | ☒ Off Exchange Direct Pay | ☒ Essential Plan (EP) |
| | ☒ Medicaid & Health and Recovery Plans (MMC/HARP) | ☒ Child Health Plus (CHP) |
| | ☐ Federal Employee Program (FEP) | ☐ Ancillary Services |
| | ☒ 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™ and generic 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® and Xromi® (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.[8,9]

**POLICY:**

Based upon our assessment and review of the peer-reviewed literature Adakveo, Endari/generic L-glutamine, 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**<br>2. Must be prescribed by, or in consultation with, a Hematologist or provider who specializes in management of SCD **AND**<br>3. Member must be at least 16 years of age **AND**<br>4. Must have documentation of ≥4 vaso-occlusive crisis (VOCs) event(s) within the preceding 12 months that required a medical facility visit (ER, clinic, hospital, local physician visit) **AND**<br>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.<br>5. Must have had (See **Table 1** for additional hydroxyurea info) **(either a, b, or c)**:<br>a. A therapeutic failure (ex. continued frequent and/or severe VOCs or ongoing, frequent transfusion requirements) to a ≥ 6 consecutive month trial of hydroxyurea at maximum tolerated dosing. Adherence will be based on:<br>i. Pharmacy refill history. If the patient does not have pharmacy benefits through this health plan, a recent pharmacy profile will be requested. Progress notes documenting usage of sample medication may also be requested **OR**<br>b. A contraindication to hydroxyurea defined as a hypersensitivity to hydroxyurea or any component of the formulation **OR**<br>c. Must have experienced **two** hematologic toxicity reactions with hydroxyurea that resulted in discontinuation of therapy.<br>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.<br>6. Adakveo will not be approved in combination with Oxbryta or Endari/generic L-glutamine as there are currently no clinical studies evaluating the combinations **AND**<br>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.<br>FDA-approved dosing: 5mg/kg IV infusion over 30 minutes at Weeks 0, 2, and every 4 weeks thereafter. |

## Endari and generic 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, b, or c)**:
    a. A therapeutic failure (ex. continued frequent and/or severe VOCs or ongoing, frequent transfusion requirements) to a ≥ 6 consecutive month trial of hydroxyurea at maximum tolerated dosing. Adherence will be based on:
        i. Pharmacy refill history. If the patient does not have pharmacy benefits through this health plan, a recent pharmacy profile will be requested. Progress notes documenting usage of sample medication may also be requested **OR**
    b. A contraindication to hydroxyurea defined as a hypersensitivity to hydroxyurea or any component of the formulation **OR**
    c. 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 kg=60 packets/30 days
    b. 30-65kg =120 packets/30 days
    c. >65kg = 180 packets/30 days
6. Endari and generic L-glutamine 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)

**On September 25, 2024, Pfizer announced that it is voluntarily withdrawing all lots of Oxbryta (voxelotor) for the treatment of sickle cell disease (SCD), in all markets where it is approved, including the United States. Pfizer has notified regulatory authorities of its decision to voluntarily withdraw Oxbryta from the market.**

This decision was based on the clinical data that now indicates the overall benefit of Oxbryta no longer outweighs the risk in sickle cell patients. The data indicates an imbalance of vaso-occulsive crises and fatal events, requiring further assessment. Patients are advised to contact their physician to discuss alternative treatment.

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntarily-withdraws-all-lots-sickle-cell-disease

**Based on the above announcement from Pfizer, The Health Plan will not authorize coverage for Oxbryta for new patients or existing users.**

| **Siklos - hydroxyurea tablets (Rx) and Xromi - hydroxyurea oral solution (Rx)** |
|---|
| 1. Must have a diagnosis of Sickle cell disease (SCD) **AND**<br>2. Must meet the following age requirement based on product being requested:<br>a. For Siklos, must be 2 years of age or older<br>b. For Xromi, must be 6 months of age or older **AND**<br>3. Must meet one of the following (a, b, or c):<br>a. Must have a valid medical reason why hydroxyurea capsules or Droxia cannot be used (i.e., unable to swallow whole capsules) **OR**<br>b. If the requested dose is exactly divisible by available strengths of hydroxyurea capsules or Droxia, the patient will be required to use those unless there is a valid medical reason, they are unable.<br>i. Hydroxyurea: 500mg capsules<br>ii. Droxia: 200mg, 300mg, 400mg capsules [NOTE: Droxia does not require prior authorization but may not be on all formularies]<br>iii. 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)<br>iv. Xromi: 100 mg/mL (148 mL bottle) **OR**<br>c. If the requested dose is not exactly divisible by available strengths of hydroxyurea capsules or Droxia, must meet both of the following (i and ii):<br>i. Must have experienced a hematologic toxicity reaction with the next highest dose that can be made by using Droxia or generic hydroxyurea capsules **AND**<br>1. 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. **AND**<br>ii. 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<br>4. Quantity Limit for Xromi: 1 bottle (148 mL) per 30 days. Upon each review and dose escalation request the allowed quantity will be reviewed in accordance with FDA-approved weight-based dosing and as such will be limited to the number of full bottles necessary to obtain the appropriate daily dose<br>Example 1: Prescriber requests Xromi 700 mg per day (7mL per day) or Siklos 700mg per day (1000mg x1/2 + 100mg x2), the patient would be required to use Droxia (300mg x1 + 400mg x1).<br>Example 2: If a prescriber requests Xromi 750 mg per day (7.5 mL per day) or 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 |

**POLICY GUIDELINES:**

1. Unless otherwise stated above within the criteria, approval time-period will be for 1 year.
   - 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.
2. Clinical documentation must be submitted for each request (initial and recertification) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments/treatment history, diagnostic testing, laboratory test results, genetic testing/biomarker results, imaging and other objective or subjective

measures of benefit which support 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.

3. 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.
4. 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 rational 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.
5. 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.
6. Not all contracts cover all Medical Infusible drugs. Refer to specific contract/benefit plan language for exclusions of Injectable Medications.
7. 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.
8. 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 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.
9. 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.

10. 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.
11. Clinical documentation must be submitted for each request (initial and recertification) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments/treatment history, diagnostic testing, laboratory test results, genetic testing/biomarker results, and imaging.
12. 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.
13. Adakveo is administered by IV infusion and is covered under the medical benefit.
14. Siklos and Endari/generic L-glutamine are orally administered and are covered under the pharmacy benefit.
15. Table 1: NIH Consensus Treatment Protocol and Technical Remarks for the Implementation of Hydroxyurea Therapy[1]
16. All requests will be reviewed to ensure they are being used for an appropriate indication and may be subject to an off-label review in accordance with our Off-Label Use of FDA Approved Drugs Policy (Pharmacy-32).
17. All utilization management requirements outlined in this policy are compliant with applicable New York State insurance laws and regulations. Policies will be reviewed and updated as necessary to ensure ongoing compliance with all state and federally mandated coverage requirements.
18. Manufacturers may either discontinue participation in, or may not participate in, the Medicaid Drug Rebate Program (MDRP). Under New York State Medicaid requirements, physician-administered drugs must be produced by manufacturers that participate in the MDRP. Products made by manufacturers that do not participate in the MDRP will not be covered under Medicaid Managed Care/HARP lines of business. Drug coverage will not be available for any product from a non-participating manufacturer. For a complete list of New/Reinstated & Terminated Labelers please visit: https://www.medicaid.gov/medicaid/prescriptiondrugs/medicaid-drug-rebate-program/newreinstated-terminated-labeler-information/index.html

**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.

Code Key:
Experimental/Investigational = (E/I),
Not medically necessary/ appropriate = (NMN).


**HCPCS:** J0791: Adakveo

**UPDATES:**

| Date | Revision |
|---|---|
| 03/05/2026 | Revised |
| 02/12/2026 | P&T Committee Review & Approval |
| 11/19/2025 | Revised |
| 08/08/2025 | Revised |
| 03/10/2025 | Revised |
| 03/06/2025 | Revised |
| 02/06/2025 | P&T Committee Review & Approval |
| 01/28/2025 | Revised |
| 12/19/2024 | Revised |
| 09/26/2024 | Revised |
| 09/13/2024 | Revised |
| 08/21/2024 | Revised |
| 06/24/2024 | Revised |
| 04/11/2024 | Revised |
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| 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 |
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| 2/11/2021 | P&T Committee Approval |
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| 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:**

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