Pharmacy Management Drug Policy

SUBJECT: Sickle Cell Disease Management
POLICY NUMBER: PHARMACY-84
ANNUAL REVIEW DATE: 12/16/2020
EFFECTIVE DATE: 12/2019
LAST REVIEW DATE: 2/21/2020

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. Medical or drug policies apply to commercial and Health Care Reform products only when a contract benefit for the specific service exists.

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]

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 ≥2 vaso-occlusive crisis (VOCs) events 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 a therapeutic failure to a minimum 6-month trial of hydroxyurea **OR**
    a. 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 as there are currently no clinical studies evaluating the combination **AND**
7. Approval will be for 6 months. Recertifications will be for 1 year and require documentation of a decrease in the number of VOCs compared to baseline.

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

Endari – L-glutamine oral powder (Rx)

1. Member must be at least 5 years old **AND**
2. Must have a diagnosis of Sickle Cell Disease type HbSS or HbS/β0 thalassemia as determined by hemoglobin electrophoresis **AND**
3. Must be experiencing symptomatic pain that is a result of Sickle Cell Disease despite a minimum 6-month trial of hydroxyurea alone at the maximum tolerated dose that resulted in treatment failure **OR**
4. Must have experienced **two** hematologic toxicity reactions with hydroxyurea that resulted in discontinuation of therapy.
    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. If a second hematologic toxicity is experienced, treatment should be discontinued.
5. Must have had serious side effects or drug failure with Nutrestore (L-glutamine oral powder, packaged as 5-gram powder packets)
6. Approval will be for one year. Recertification will require documentation of improvement in Sickle Cell Disease related pain and adherence to the approved regimen.
7. QL of 180/30

Oxbryta – 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 12 years of age **AND**
4. Baseline hemoglobin must be ≥5.5 to ≤10.5 g/dL (measured within 60 days) **AND**
5. Must have documentation of ≥2 vaso-occlusive crisis (VOCs) events 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 a therapeutic failure to a minimum 6-month trial of hydroxyurea **OR**
    a. 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.
7. Oxbryta will not be approved for use in combination with Adakveo as there are currently no clinical studies evaluating the combination **AND**
8. Approval will be for 6 months. Recertification will be for 1 year and require a ≥1 g/dL increase in hemoglobin compared to baseline (measured within 60 days). Subsequent yearly recertifications will require documentation of hemoglobin levels maintained ≥1 g/dL compared to baseline.

Siklos – hydroxyurea tablets (Rx)

1. Must have a diagnosis of sickle cell anemia
2. Must be between the ages of 2 and 18 years old
3. Must have had serious side effects with the next highest (or equivalent) dose that can be made by using Droxia or generic hydroxyurea capsules
4. Must have had drug failure with the next lowest (or equivalent) dose that can be made by using Droxia or generic hydroxyurea capsules

Siklos is available as a 1000 mg tablet that can be split into quarters, so doses of 250 mg, 500 mg, 750 mg, or 1000 mg can be derived from a single tablet. An example of the above criteria: If a prescriber requests Siklos 750 mg per day, the patient would be required to have serious side effects with two 400 mg capsules taken together to make 800 mg per day **AND** drug failure with two 300 mg capsules taken together to make 600 mg per day

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. Prior-authorization is contract dependent.
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 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.
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. 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.
6. 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.

7. 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.
8. Adakveo is administered by IV infusion and is covered under the medical benefit.
9. Siklos, Endari, and Oxbryta are orally administered and are covered under the pharmacy benefit.

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:
Not yet assigned

UPDATES:

Date	Revision
2/21/2020	Revised
2/13/2020	P&T 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; November 2019.

8. Siklos® tablets [prescribing information]. Bryn Mawr, PA: Medunik USA Inc; May 2018.