Droxia and Siklos Prior Authorization Program Summary

This program applies to Medicaid.

For Medicaid, the preferred agents are the MN Medicaid Preferred Drug List (PDL) preferred drug: Droxia

The BCBS MN Step Therapy Supplement also applies to this program for Medicaid.

FDA APPROVED INDICATIONS[1,4]

Agent(s)	Indication(s)
Droxia® (hydroxyurea) capsule	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® (hydroxyurea) tablet	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.

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

CLINICAL RATIONALE

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 effects 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]

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 hemoglobin-F (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]

Efficacy

The efficacy of hydroxyurea in sickle cell anemia was assessed in a randomized, double-blind, placebo-controlled trial that evaluated 299 adult patients (≥18 years) with moderate to severe disease (≥3 painful crises yearly). A painful crisis was defined in the study as acute sickling-related pain that resulted in a visit to a medical facility, that lasted more than 4 hours, and that required treatment with a parenteral narcotic or NSAID. Chest syndrome, priapism, and hepatic sequestration were also included in this definition. The trial was stopped by the Data Safety Monitoring Committee, after accrual was completed but before the scheduled 24 months of follow-up was completed in all patients, based on observations of fewer painful crises among patients receiving hydroxyurea.[1]

Compared to placebo treatment, treatment with hydroxyurea resulted in a significant decrease in the yearly rate of painful crises, the yearly rate of painful crises requiring hospitalization, the incidence of chest syndrome, the number of patients transfused, and units of blood transfused. Hydroxyurea treatment significantly increased the median time to both first and second painful crises.[1]

The efficacy of Siklos was assessed in the European Sickle Cell Disease Cohort study (ESCORT HU), an open-label single-arm study of 405 pediatric patients with sickle cell disease from 2-18 years of age, of which 141 had not been previously treated with hydroxyurea prior to enrollment. Evaluable patients had at least 12 months follow-up (median [range] 23 months [12,80]). Median (range) hemoglobin F percentages were 5.6% (1.3, 15.0) at baseline and 12.8% (2.1, 37.2) at least 6 months (the value closest to 6 months collected between 5 and 14 months) after initiation of Siklos treatment, with median (range) change of 5.9% (-2.2, 34.7) in 47 patients. Median (range) hemoglobin levels were 8.2 g/dL (3.7, 14.2) at baseline, 8.8 g/dL (0.7, 13.1) at 6 months (the value closest to 6 months collected between 5 and 7 months), and 8.9 g/dL (5.5, 13.2) at 12 months (the value closest to 12 months collected between 10 and 14 months) after initiation of Siklos treatment. The median (range) change was 0.5 g/dL (-4.6, 6.1) in 63 patients at 6 months (the post-baseline value closest to 6 months collected between 5 and 7 months) and 0.7 g/dL (-6.4, 6.0) in 83 patients at 12 months (the post-baseline value closest to 12 months collected between 10 and 14 months) after initiation of Siklos treatment.[4]

Safety

Droxia and Siklos carry the following black box warnings:[1,4]

- May cause severe myelosuppression. Do not give if bone marrow function is markedly depressed. Monitor blood counts at baseline and throughout treatment. Interrupt treatment and reduce dose as necessary.
- Hydroxyurea is carcinogenic. Advise sun protection and monitor patients for malignancies.

References

1. Droxia prescribing information. Bristol-Myers Squibb Company. January 2022.
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. Siklos prescribing information. Medunik. December 2021.

Droxia and Siklos Prior Authorization

TARGET AGENT(S)

For Medicaid, the preferred agents are the MN Medicaid Preferred Drug List (PDL) preferred drug: Droxia

Droxia® (hydroxyurea)
Siklos® (hydroxyurea)

Brand (generic)	GPI	Multisource Code
Droxia (hydroxyurea)		
200 mg capsule	82803030000120	M, N, O, and Y
300 mg capsule	82803030000130	M, N, O, and Y
400 mg capsule	82803030000140	M, N, O, and Y
Siklos (hydroxyurea)		
100 mg tablet	82803030000320	M, N, O, and Y
1,000 mg tablet	82803030000340	M, N, O, and Y

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Initial Evaluation
Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
    a. Information has been provided that indicates the patient has been treated with the requested agent within the past 90 days
    OR
    b. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed
    OR
    c. The patient has an FDA approved indication for the requested agent and route of administration
    OR
    d. The patient has another indication that is supported in compendia for the requested agent and route of administration

    AND
2. ONE of the following:
    a. The patient's age is within FDA labeling for the requested indication for the requested agent
    OR
    b. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication

    AND
3. ONE of the following:
    a. The requested agent is Droxia
    OR
    b. The request is Siklos and ONE of the following:
        i. The patient is currently being treated with the requested agent as indicated by ALL of the following:
            1. A statement by the prescriber that the patient is currently taking the requested agent
            AND

2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
   AND
3. The prescriber states that a change in therapy is expected to be ineffective or cause harm

OR

ii. The patient's medication history includes Droxia AND ONE of the following:
   1. The patient had an inadequate response to Droxia
      OR
   2. The prescriber has submitted an evidence-based and peer reviewed clinical practice guideline supporting the use of Siklos over Droxia

OR

iii. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to Droxia

OR

iv. The prescriber has provided documentation that Droxia cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

OR

v. The prescriber has submitted documentation supporting the use of Siklos over Droxia (e.g., unable to appropriately dose Droxia for pediatric patient)

AND

4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
5. The patient will NOT be using the requested agent in combination with another agent included in this program for the requested indication
   AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
7. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication

Compendia Allowed: AHFS, or DrugDex 1 or 2a level of evidence
Length of Approval: 12 months

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
   AND
2. The patient has had clinical benefit with the requested agent (e.g., decrease in frequency of painful crises)

AND

3. The prescriber is a specialist in the area of the patient's diagnosis (e.g. hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis
   AND
4. The patient will NOT be using the requested agent in combination with another agent included in this program for the requested indication
   AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
6. The requested quantity (dose) does not exceed the maximum FDA labeled dose for the requested indication

Length of Approval: 12 months