LOUISIANA BLUE

Siklos® (hydroxyurea)

Policy # 00649
Original Effective Date: 11/21/2018
Current Effective Date: 05/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider Siklos®‡ (hydroxyurea) for the treatment of sickle cell anemia to be **eligible for coverage**** when the patient selection criteria are met**.**

Patient Selection Criteria

Coverage eligibility for Siklos (hydroxyurea) will be considered when the following criteria are met:

- Patient has a diagnosis of sickle cell anemia; AND
- Patient is greater than or equal to 2 years of age; AND
- The requested dose of Siklos CANNOT be obtained using other commercially available hydroxyurea products (either alone or in combination). Note that hydroxyurea is available as 500 milligram (mg) generic hydroxyurea capsules and as 200, 300, and 400 mg Droxia®‡ capsules.
  *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*

When Services Are Considered Not Medically Necessary

The use of Siklos (hydroxyurea) when the requested dose can be obtained using another commercially available hydroxyurea product is considered to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Siklos (hydroxyurea) for conditions other than sickle cell anemia or for use in patients younger than 2 years of age to be **investigational.***

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Background/Overview

Siklos is a formulation of hydroxyurea that is supplied as 100 mg and 1000 mg tablets. It is one of three hydroxyurea products available in the United States. Hydrea®‡ and its generic is a formulation available in 500 mg capsules that is FDA-approved for the treatment of resistant chronic myeloid leukemia and locally advanced squamous cell carcinomas of the head and neck. Droxia is a formulation available in 200, 300, and 400 mg capsules that is FDA-approved 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. For sickle cell disease, hydroxyurea should be dosed based on patient weight and blood count regardless of the specific product used. Of note, Siklos is the only product that can be dissolved in water and administered as a liquid. The other products are capsules that must be swallowed whole.

The 2014 National Institutes of Health- National Heart, Lung, and Blood Institute Evidence-based management of sickle cell disease guidelines recommend hydroxyurea therapy in adult patients with three or more sickle cell-associated moderate to severe pain crises in a 12-month period, who have sickle-cell associated pain that interferes with daily activities and quality of life, who have severe and/or recurrent acute chest syndrome, or who have severe symptomatic chronic anemia. The guidelines also recommend hydroxyurea for infants $\geq$9 months of age, children, and adolescents with sickle cell anemia to reduce complications.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Siklos is indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in adult and pediatric patients, 2 years of age and older, with sickle cell anemia with recurrent moderate to severe painful crises.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Siklos in pediatric patients was assessed in the European Sickle Cell Disease Cohort study, an open-label, single-arm study that included 405 pediatric patients with sickle cell disease from 2-18 years of age. 141 of these patients had not been previously treated with hydroxyurea prior to enrollment. Evaluable patients had at least 12 months of follow up. Median hemoglobin F percentages were 5.6% at baseline and 12.8% at least 6 months after initiation of Siklos treatment with a median change of 5.9% in 47 patients. Median hemoglobin levels were 8.2 g/dL at baseline,

8.8 g/dL at 6 months, and 8.9 g/dL at 12 months after initiation of Siklos treatment. Among pediatric patients not previously treated with hydroxyurea prior to enrollment and analyzable for efficacy, the percentage of patients with at least one vaso-occlusive episode, one episode of acute chest syndrome, one hospitalization due to sickle cell disease, or one blood transfusion decreased after 12 months of Siklos treatment.

The efficacy of Siklos for adult use was also assessed in the European Sickle Cell Disease Cohort study. This study included 1,077 adults, of which 436 were naïve to hydroxyurea treatment. Of these, there were 370 evaluable patients with at least 12 months of follow-up data. In this group, the incidence and number of vaso-occlusive events, hospitalizations, acute chest syndrome, and blood transfusions decreased over 12 months of Siklos treatment.

References

1. Siklos [package insert]. Medunik. Bryn Mawr, PA. Updated March 2022.
2. Hydrea [package insert]. Bristol-Myers Squibb. Princeton, NJ. Updated December 2017.
3. Droxia [package insert]. Bristol-Myers Squibb. Princeton, NJ. Updated December 2017.

Policy History

Original Effective Date: 11/21/2018
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11/08/2018	Medical Policy Committee review
11/21/2018	Medical Policy Implementation Committee approval. New policy.
11/07/2019	Medical Policy Committee review
11/13/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. Removed upper limit of age requirement to reflect FDA approval for use in adults.
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. No change to coverage.
04/04/2024	Medical Policy Committee review
04/10/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

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04/03/2025 Medical Policy Committee review
04/09/2025 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 04/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.