Clinical Policy Title:	hydroxyurea
Policy Number:	RxA.281
Drug(s) Applied:	Siklos®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Hydroxyurea (Siklos®) is an antimetabolite. It is indicated to 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
Hydroxyurea (Siklos®)	Sickle cell disease	Initial dose 20 mg/kg PO once daily. Dose may be increased by 5 mg/kg/day every 8 weeks or sooner if a severe painful crisis occurs. Renal impairment: Reduce dose by 50% in patients with creatinine clearance less than 60 mL/min	35 mg/kg/day (maximum dose based on weight)

Dosage Forms

- Tablets: 100 mg, 1,000 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Sickle Cell Disease (must meet all):

1. Diagnosis of sickle cell disease;
2. Age ≥ 2 years;
3. Documentation supports inability to use generic hydroxyurea (e.g., contraindications to the excipients in

generic hydroxyurea);
4. Dose does not exceed 35 mg/kg per day based on weight.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Oncology Indications (off-label) (must meet all):
1. Diagnosis of one of the following (a, b, c, or d);
   a. Acute myeloid leukemia;
   b. Chronic myeloid leukemia;
   c. Head and neck cancer;
   d. Myeloproliferative neoplasms (myelofibrosis, polycythemia vera, essential thrombocythemia);
   e. Histiocytic neoplasms (Langerhans Cell Histiocytosis)
2. Age ≥ 2 years;
3. Documentation supports inability to use generic hydroxyurea (e.g., contraindications to the excipients in generic hydroxyurea);
4. Request meets one of the following (a or b):
   a. Dose does not exceed 80 mg/kg per day based on weight;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. **All Indications in Section I** (must meet all)**:**
1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a, b, or c):
   a. Sickle cell disease: new dose does not exceed 35 mg/kg per day based on weight;
   b. Oncology indications: new dose does not exceed 80 mg/kg per day based on weight;
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
hydroxyurea (Hydrea®, Droxia®)	Sickle cell disease: 15 mg/kg PO once daily CML: 40 mg/kg/day. Head and neck cancer: 1,000 mg q12h.	Sickle disease: 35 mg/kg/day Oncology indications: 80 mg/kg/day

Therapeutic alternatives are listed as Brand name®(generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Hypersensitivity to hydroxyurea or any other component of its formulation.

- Boxed Warning(s):
  - Myelosuppression – Siklos® may cause sever 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.
  - Malignancies – Hydroxyurea is carcinogenic. Advise sun protection and monitor patients for malignancies.

APPENDIX D: General Information

- Sickle cell disease is an inherited disease that affects the red blood cells. Children with the disease have abnormal red blood cells that are stiff and half-moon-shaped, causing them to become stuck in the blood vessels, blocking blood flow. These blockages can cause crippling pain and organ damage, which require hospitalization.
- Science does not fully understand how hydroxyurea works, but studies suggest that it increases the amount of fetal hemoglobin (HbF), as well as the amount of water, in red blood cells. In this way, Siklos® helps keep children's red blood cells round and flexible so they can travel more easily through the blood vessels. This may help reduce painful crises and some of the complications of the disease.

References

1. Siklos Prescribing Information. Bryn Mawr, PA: Medunik USA, Inc.; May 2019. Available at https://www.siklosusa.com/. Accessed May 5, 2021.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; Dec, 2017. Available at: http://www.clinicalpharmacology-ip.com. Accessed May 5, 2021.
3. Lexicomp Online [Internet Database]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc. Updated periodically. Accessed May 5, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Drug(s) Applied was updated. 3. Line of Business Policy Applies to was updated.	07/02/2020	09/14/2020

4. Continued Therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance..." 5. Commercial approval duration and Medicaid approval duration updated. 6. Updated APPENDIX C: Contraindications to include “hydroxyurea or any other component of its formulation” and Boxed Warnings to include Myelosuppression and Malignancies. 7. Updated dosing information to include renal impairment dosing “Reduce dose by 50% in patients with creatinine clearance less than 60 mL/min”. 8. References were updated.		
Policy was reviewed: 1. Initial approval criteria was updated: Off-label indication “Histiocytic neoplasms (Langerhans Cell Histiocytosis)” was added to I.B.1. 2. Statement about provider sample, ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 3. Appendix B: Therapeutic Alternatives header verbiage was changed to “Below are suggested therapeutic alternatives based on...” 4. Appendix D was updated. 5. References were updated.	05/05/2021	06/10/2021