Clinical Policy: Hydroxyurea (Siklos, Xromi)

Reference Number: CP.PMN.193
Effective Date: 02.19.19
Last Review Date: 05.24
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Hydroxyurea (Siklos®, Xromi®) is an antimetabolite.

FDA Approved Indication(s)

Siklos and Xromi are indicated to reduce the frequency of painful crises and reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises for the following ages:

- Siklos: adult and pediatric patients 2 years of age and older
- Xromi: pediatric patients 6 months to less than 2 years of age

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Siklos and Xromi are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Sickle Cell Disease (must meet all)**:**

1. Diagnosis of sickle cell disease (SCD);
2. Age is one of the following (a or b):
   a. For Siklos: ≥ 9 months;
   b. For Xromi: ≥ 6 months and < 2 years;
3. For members aged ≥ 2 years: Member must use generic hydroxyurea, unless contraindicated or clinically significant adverse effects are experienced;
4. Dose does not exceed 35 mg/kg per day based on weight.

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Oncology Indications (off-label) (must meet all)**:**

1. Diagnosis of one of the following (a-f);
   a. Acute myeloid leukemia;
   b. Chronic myeloid leukemia;
   c. Head and neck cancer;
   d. Myeloproliferative neoplasms (myelofibrosis, polycythemia vera, essential thrombocythemia);

e. Myelodysplastic syndromes;
f. Langerhans cell histiocytosis;
2. Request is for Siklos;
3. Age ≥ 2 years;
4. Member must use generic hydroxyurea, unless contraindicated or clinically significant adverse effects are experienced;
5. 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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
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. SCD: New dose does not exceed 35 mg/kg per day based on weight;
   b. For Siklos in oncology indications: one of the following (i or ii): *
      i. New dose does not exceed 80 mg/kg per day based on weight;

ii. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
NHLBI: National Heart, Lung, and Blood Institute
SCD: sickle cell disease

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
hydroxyurea (Hydrea®, Droxia®)	SCD: 15 mg/kg PO QD CML: 40 mg/kg/day Head and neck cancer: 1,000 mg q12h	SCD: 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 and malignancies

Appendix D: General Information

- Per the 2014 NHLBI Evidence-based management of SCD Expert Panel Report, for infants 9 months of age and older, children, and adolescents with SCD, treatment with hydroxyurea should be offered regardless of clinical severity to reduce SCD-related complications. The starting dose for infants and children is 20 mg/kg/day.

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Hydroxyurea (Siklos)	Initial dose 15 mg/kg in adults and 20 mg/kg in children PO QD based on patient's actual or ideal weight, whichever is less. Dose may be increased by 5 mg/kg/day every 8 weeks or sooner if a severe painful crisis occurs.	35 mg/kg/day
Hydroxyurea (Xromi)	Initial dose 15 mg/kg (rounded to nearest 10 mg) PO QD based on the patient's actual body weight. Dose may be increased by 5 mg/kg/day every 8 to 12 weeks.	35 mg/kg/day

VI. Product Availability

Drug Name	Availability
Hydroxyurea (Siklos)	Oral tablets: 100 mg, 1,000 mg
Hydroxyurea (Xromi)	Oral solution: 100 mg/mL in a 150 mL multiple-dose bottle

VII. References

1. Siklos Prescribing Information. Bryn Mawr, PA: Medunik USA, Inc.; November 2023. Available at https://files.medunik.com/usa/siklos/prescribing-information.pdf. Accessed January 16, 2024.
2. Xromi Prescribing Information. Leicester, UK: Nova Laboratories Ltd.; April 2024. Available at: https://xromi-us.com/pi/. Accessed May 20, 2024.
3. Lexicomp Online [Internet Database]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc. Updated periodically. Accessed February 11, 2024.
4. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed February 11, 2024.
5. Brandow A, Carroll C, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. *Blood Advances*. 2020;4(12):2656-2701.

6. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Evidence-based management of sickle cell disease: Expert Panel Report, 2014. National Heart, Lung, and Blood Institute (NHLBI). Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2020 annual review: no significant changes; applied HIM line of business; references reviewed and updated	02.13.20	05.20
2Q 2021 annual review: myelodysplastic syndromes added as option for off-label oncology indication per NCCN-supported category 2A recommendation; references for HIM line of business off-label use revised from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	02.01.21	05.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less; RT4: updated FDA approved indication to reflect adult expansion for sickle cell anemia.	12.16.21	02.22
2Q 2022 annual review: Langerhans Cell Histiocytosis added as option for off-label oncology indication per NCCN-supported category 2A recommendation; references reviewed and updated.	02.06.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.05.22	
2Q 2023 annual review: no significant changes; references reviewed and updated.	02.03.23	05.23
2Q 2024 annual review: revised age criterion to age ≥ 9 months given guideline support and lack of availability and/or access to age-appropriate hydroxyurea formulation; clarified that generic hydroxyurea trial applies to members age ≥ 2 years; references reviewed and updated.	03.05.24	05.24
RT4: added newly approved Xromi formulation; added clarification that for off-label oncology use request is for Siklos and template language that prescribed regimen is FDA-approved or recommended by NCCN.	05.20.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.