Pharmacy Policy Bulletin: J-0777 Branded Hydroxyurea Products – Commercial and Healthcare Reform	
Number: J-0777	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial (1.):** 1. Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform**: Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0777-006	**Original Date:** 01/31/2018
Effective Date: 04/25/2025	**Review Date:** 04/09/2025

Drugs Product(s):	• Siklos (hydroxyurea) oral tablets • Xromi (hydroxyurea) oral solution

FDA-Approved Indication(s):	• Siklos
	  ○ 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 (SCA) with recurrent moderate to severe painful crises
	• Xromi
	  ○ To reduce the frequency of painful crises and reduce the need for blood transfusions in pediatric patients aged 6 months of age and older with sickle cell anemia with recurrent moderate to severe painful crises.

Background:	• It is hypothesized that hydroxyurea inhibits DNA synthesis, thus exerting antineoplastic effects. The mechanism by which it provides beneficial effects in SCA is unknown. Known pharmacologic effects that may contribute to SCA improvement include: increase in hemoglobin F in red blood cells (RBCs), decrease in neutrophils, increase in water content of RBCs, increase in deformability of sickled cells, and alteration in the adhesion of RBCs to endothelium. • Other formulations of hydroxyurea for SCD include Droxia (hydroxyurea) oral capsules, Hydrea (hydroxyurea) oral capsules, and Siklos (hydroxyurea) oral tablets. • Droxia, Siklos, and Xromi are orally administered antimetabolites used 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. Siklos are available for patients ≥ 2 years of age and Droxia is available for patients ≥ 18 years of age. Xromi is the only formulation of hydroxyurea, and the only SCD therapy, approved for use in pediatric patients < 2 years of age. Hydrea does not have these indications for SCD but is commonly used off-label. • Hydroxyurea and Hydrea are available in 500 mg capsules, while Droxia is available in 200 mg, 300 mg, and 400 mg capsules. Siklos is available in 100 mg and 1,000 mg tablets. None of the tablets or capsules should be crushed or opened because of the cytotoxic nature of hydroxyurea. Generic hydroxyurea

	tablets can be extemporaneously compounded into an oral solution, but Xromi is the only hydroxyurea oral solution available on the market. • The National Heart, Lung, and Blood Institute Expert Panel report recommends hydroxyurea in adults with SCA who have sickle cell-associated pain that interferes with daily activities and quality of life, who have a history of severe and/or recurrent ACS, and 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, treatment with hydroxyurea should be offered, regardless of clinical severity to reduce complications. • Prescribing Considerations: ○ Blood counts should be monitored regularly with use of hydroxyurea.

Approval Criteria

I. Initial Authorization

When a benefit, Siklos or Xromi may be approved when all of the following criteria are met **(A. through E.)**:

A. The member meets one (1) of the following criteria **(1. or 2.)**:
  1. If the request is for Siklos, the member is 2 years of age or older.
  2. If the request is for Xromi, the member is 6 months to 17 years of age.

B. The member has a diagnosis of sickle cell anemia (specifically, sickle cell disease) (ICD-10: D57).

C. The prescriber attests that the member is experiencing painful, recurrent sickle cell crises.

D. The member has experienced therapeutic failure or intolerance to plan-preferred, generic hydroxyurea.

E. If the request is for Xromi, the member has an inability to swallow tablets.

II. Reauthorization

When a benefit, reauthorization of Siklos or Xromi may be approved when all of the following criteria are met **(A. and B.)**:

A. If the request is for Xromi, the member is 17 years of age or less.

B. The member meets one (1) of the following criteria **(1. or 2.)**:
  1. The member has experienced a reduction in painful sickle cell crises.
  2. The member has experienced a reduction in blood transfusions.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None.

References:

1. Siklos (hydroxyurea) [prescribing information]. France: Addmedica; November 2023.
2. Droxia (hydroxyurea) [prescribing information]. Princeton, NJ: ER Squibb and Sons; November 2023.
3. DRUGDEX System (Micromedex 2.0). Greenwood Village, CO: Truven Health Analytics; 2024.
4. Hydrea [package insert]. Griefswald, Germany: Cheplapharm; December 2023.
5. Xromi [package insert]. Leicester, United Kingdom: Novo Labs LTD; December 2024.
6. Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Adv. 2020;4(12):2656-2701.
7. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. *Blood Adv*. 2021;5(18):3668-3689.
8. Chou ST, Alsawas M, Fasano RM, et al. American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support. *Blood Adv*. 2020;4(2):327-355.
9. DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv*. 2020;4(8):1554-1588.
10. Liem RI, Lanzkron S, D Coates T, et al. American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease. *Blood Adv*. 2019;3(23):3867-3897.
11. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. *JAMA*. 2014 Sep 10;312(10):1033-48.
12. Evidence-Based Management of Sickle Cell Disease. U.S. Department of Health and Human Services National Institute of Health. Available at: https://www.nhlbi.nih.gov/health-topics/evidence-based-management-sickle-cell-disease. Accessed February 21, 2024.