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Drug Class Literature Scan: Drugs for Sickle Cell Disease

Date of Review: April 2022

Date of Last Review: June 2020
Literature Search: 05/01/20 – 12/23/21

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- One new clinical practice guideline and an expanded indication for voxelotor was identified in this drug class literature scan.
- Guidance from the National Institute for Health and Care Excellence (NICE) recommends crizanlizumab for use in patients with sickle cell disease (SCD) who are 16 years or older for prevention of recurrent vaso-occlusive crises (VOCs) (history of 2 or more) in the previous 12 months.[1]
- Voxelotor received an expanded indication for the treatment of SCD in pediatric patients 4 years of age and older.[2] One small, single-arm, open-label trial demonstrated that 36% of patients 4 years of age to less than 12 years of age treated with voxelotor experienced an increase in hemoglobin [Hb] of 1 g/dL or greater from baseline to week 24 (95% confidence interval [CI], 21.6% to 49.5%).[2]
- The hydroxyurea formulation, Siklos, was approved for the expanded indication for use in adult patients for the reduction in the frequency of painful crises and need for blood transfusions in patients with SCD with recurrent moderate to severe painful crises. Approval was based on observational, cohort data with small changes in efficacy outcomes.[3]
- The Food and Drug Administration (FDA) updated safety warnings and precautions for 2 drugs in the SCD drug class. Hemolytic anemia is associated with patients who use hydroxyurea and long-term use of hydroxyurea has demonstrated a risk of secondary leukemia.[4] Crizanlizumab prescribing information was updated with a risk of infusion-related reactions that may be severe and require hospitalization.[5]

Recommendations:
- No changes to the preferred drug list (PDL) are recommended based on the evidence review.
- Update prior authorization (PA) criteria to include the expanded age indication for voxelotor.
- After evaluation of costs in executive session, no PDL changes were recommended.

Summary of Prior Reviews and Current Policy
- The SCD drug class was last reviewed in June 2020.
- Hydroxyurea capsules (generic formulation only) were added as a preferred treatment and voxelotor and crizanlizumab were designated as non-preferred. L-glutamine maintained non-preferred status and the PA was amended to include l-glutamine products.

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Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2**. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
No new high-quality systematic reviews were identified.

After review, 8 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). [6–13]

New Guidelines:

<u>NICE – Crizanlizumab for Preventing Sickle Cell Crises in Sickle Cell Disease</u>
New guidance from NICE on the use of crizanlizumab for SCD was published 2021.[1] Evaluation of the evidence was based on the SUSTAIN[14] trial which found that crizanlizumab may reduce the number of sickle cell crises compared to supportive care, with or without hydroxyurea. NICE found insufficient evidence on the long-term benefits of crizanlizumab. NICE requires requests for crizanlizumab be reviewed by specialists and according to labeling.

Recommendations for use of crizanlizumab:
- An option for preventing recurrent VOC in patients 16 years of age or older with SCD.[1]
- Patients will be eligible who meet the following criteria:
    - Confirmed diagnosis of SCD
    - Age of 16 years or older with a history of 2 or more VOCs in the previous 12 months

New Indications:
<u>Voxelotor (Oxbryta):</u> In December 2021, voxelotor received an expanded indication for the use in pediatric patients 4 years of age and older.[2] The indication was based off data from patients with SCD ages 4 to less than 12 years in a small (n=45) open-label, , single arm, phase 2 trial. There were an additional 11 patients who were aged 12 to less than 17 years. Inclusion criteria required patients to have a baseline Hb of less than or equal to 10.5 g/dL. The HbSS or HbS/beta^0-thalassemia genotype was present in every patient. The dose of voxelotor was based on weight and given as 600 mg, 900 mg, or 1,500 mg once daily for patients weighing 10 kg to less than 20 kg, 20 kg to less than 40 kg, or 40 kg or greater, respectively.[2] Doses were provided as tablets to be used in an oral suspension. Voxelotor doses of 1,500 mg day were given to patients 12 to less than 17 years of age. Stable doses of hydroxyurea were allowed as background therapy and

utilized by 80% of participants. The trial demonstrated that 36% of patients 4 years of age to less than 12 years of age treated with voxelotor experienced an increase in hemoglobin [Hb] of 1 g/dL or greater from baseline to week 24 (95% confidence interval [CI], 21.6% to 49.5%).[2]

Hydroxyurea (Siklos): Hydroxyurea received an expanded indication in December 2021 for the use in adult patients to reduce the frequency of painful crises and to reduce the need for blood transfusions in those with sickle cell anemia with recurrent moderate to severe painful crises.[15] Approval was based off of one, observational, phase IV, cohort study in 1906 adult participants. Changes in vaso-occlusive crises last >48 hours, acute chest syndrome episodes, hospitalizations and the percentage of patients requiring blood transfusions within three first 12 months were compared to the previous 12 months. In comparison to 12 months prior, vaso-occlusive crises were reduced by 0.9 episodes ($p<0.05$), acute syndromes by 0.2 ($p<0.05$), hospitalizations by 0.6 ($p<0.05$), number of days of hospitalizations for SCD by 3.7 days ($P<0.05$) and number of patients with at least one blood transfusion by 223 patients ($p<0.001$).[3] Neutropenia (4%) and thrombocytopenia (5%) were the most common adverse reactions.[3]

New FDA Safety Alerts:

Table 1. Description of New FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Hydroxyurea[4,15]	Droxia / Siklos	July 2021	Warnings and precautions	Hemolytic anemia has been reported in patients taking hydroxyurea. Acute jaundice or hematuria in the presence of worsening anemia may be indicative of hemolysis and patients should be evaluated. Hydroxyurea should be discontinued if confirmed diagnosis of hemolytic anemia is made.
Hydroxyurea[4]	Droxia	February 2021	Warnings and Precautions	Secondary leukemia has been reported with long-term use of hydroxyurea in patients with sickle cell disease. Patients who use hydroxyurea on a long-term basis should have regular blood counts performed to monitor for leukemia.
Crizanlizumab[5]	Adakveo	July 2021	Warnings and precautions	Infusion-related reactions, including severe pain and potentially hospitalization have been reported. Monitor patients for infusion-related reactions (e.g., headache, pain in various locations, fever, chills, nausea, vomiting, diarrhea, fatigue, dizziness, pruritus, uticaria, sweating, shortness of breath or wheezing) and discontinue if reactions are severe.

References:

1. National Institute for Health and Care Excellence. Crizanlizumab for Preventing Sickle Cell Crises in Sickle Cell Disease. Technology Appraisal Guidance. November 2021.

2. Oxbryta (voxelotor) [product information]. Global Blood Therapeutics, Inc., South San Franscisco, CA. November 2019.

3. de Montalembert M, Voskaridou E, Oevermann L, et al. Real-Life Experience with Hydroxyurea in Patients with Sickle Cell Disease: Results from the Prospective ESCORT-HU Cohort Study. *Am J Hematol*. 2021;96(10):1223-1231. doi:10.1002/ajh.26286

4. Droxia (hydroxyurea) [product information]. Princeton, NJ: Bristol-Myers Squibb Company. July 2021.

5. Adakveo (crizanlizumab-tmca) [product Information]. Novartis Pharamaceuticals Corporation, East Hanover, NJ. November 2019.

6. Wadman RI, Pol WL van der, Bosboom WM, et al. Drug Treatment for Spinal Muscular Atrophy Types II and III. *Cochrane Database of Systematic Reviews*. 2020;(1). doi:10.1002/14651858.CD006282.pub5

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8. Thom H, Jansen J, Shafrin J, et al. Crizanlizumab and Comparators for Adults with Sickle Cell Disease: a Systematic Review and Network Meta-analysis. *BMJ Open*. 2020;10(9):e034147. doi:10.1136/bmjopen-2019-034147

9. Ryan N, Dike L, Ojo T, et al. Implementation of the Therapeutic use of Hydroxyurea for Sickle Cell Disease Management in Resource-constrained Settings: a Systematic Review of Adoption, Cost and Acceptability. *BMJ Open*. 2020;10(11):e038685. doi:10.1136/bmjopen-2020-038685

10. Shih S, Cohen LL. A Systematic Review of Medication Adherence Interventions in Pediatric Sickle Cell Disease. *Journal of Pediatric Psychology*. 2020;45(6):593-606. doi:10.1093/jpepsy/jsaa031

11. Hasson C, Veling L, Rico J, Mhaskar R. The Role of Hydroxyurea to Prevent silent Stroke in Sickle Cell Disease: Systematic Review and Meta-analysis. *Medicine*. 2019;98(51):e18225. doi:10.1097/MD.0000000000018225

12. Cieri-Hutcherson NE, Hutcherson TC, Conway-Habes EE, et al. Systematic Review of l-glutamine for Prevention of Vaso-occlusive Pain Crisis in Patients with Sickle Cell Disease. *Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy*. 2019;39(11):1095-1104. doi:10.1002/phar.2329

13. Tanriverdi LH, Sarici A, Erkurt MA, Parlakpinar H. The Efficacy of Voxelotor, 900 mg in patients with Sickle Cell Anaemia: A Meta-analysis of the Randomised Controlled Trials. *Int J Clin Pract*. 2021;75(6):e13967. doi:10.1111/ijcp.13967

14. Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. *New England Journal of Medicine*. 2017;376(5):429-439. doi:10.1056/NEJMoa1611770

15. Siklos (hydroxyurea) [product information]. Bryn Mawr, PA: Medunik USA. December 2021.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
hydroxyurea	HYDREA	CAPSULE	Y
hydroxyurea	HYDROXYUREA	CAPSULE	Y
hydroxyurea	HYDROXYUREA	CAPSULE	Y
glutamine	ENDARI	POWD PACK	N
hydroxyurea	DROXIA	CAPSULE	N
hydroxyurea	SIKLOS	TABLET	N
crizanlizumab-tmca	ADAKVEO	VIAL	N
voxelotor	OXBRYTA	TABLET	N

Appendix 2: New Comparative Clinical Trials

A total of 64 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to December 23, 2021

Search Strategy:

#	Searches	Results
1	hydroxyurea.mp. or Hydroxyurea/	12708
2	glutamine.mp. or Glutamine/	46513
3	crizanlizumab.mp.	50
4	voxelotor.mp.	72
5	1 or 2 or 3 or 4	59243
6	limit 5 to (english language and humans and yr="2020 -Current")	1745
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	64

Appendix 4: Key Inclusion Criteria

Population	Patients with sickle cell disease
Intervention	Therapies for sickle cell
Comparator	Placebo or active treatment
Outcomes	Hemoglobin response, blood transfusions, stroke, vaso-occlusive crisis, hospitalizations, pain scores
Timing	Symptom onset
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

Sickle Cell Anemia Drugs

Goal(s):

- Approve the use of drugs for sickle cell disease for medically appropriate indications funded by the OHP.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs or non-preferred formulations (pharmacy administered claims)
- Crizanlizumab (pharmacy or provider administered claims)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a renewal request for voxelotor, crizanlizumab or l-glutamine (ENDARI)?	**Yes:** Go to renewal criteria below.	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products/formulations do not require PA. • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #6
6. Has the patient received a 3-month trial of hydroxyurea at stable doses or have contraindications to hydroxyurea?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; Recommend trial of hydroxyurea (stable dose for 3 months)
7. Is the request for voxelotor and the patient is 4 years or older?	**Yes:** Go to #8	**No:** Go to #9
8. Does the patient have a hemoglobin level of 10.5 g/dL or less?	**Yes:** Approve for up to 6 months. Record baseline hemoglobin value.	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the request for crizanlizumab and the patient is 16 years or older?	**Yes:** Go to #10	**No:** Go to #11
10. Has the patient had at least 2 pain crises in the last 12 months?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the request for L-glutamine (ENDARI) and the patient is 5 years or older?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Has the patient had at least 2 pain crises in the last 12 months?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is the request for a first renewal of voxelotor?	**Yes**: Go to #2	**No:** Go to #4
2. Has the patient had an increase in hemoglobin from baseline hemoglobin level since starting voxelotor?	**Yes:** Approve for up to 12 months.	**No:** Go to #3
3. Is the request for subsequent renewals (renewals beyond the first year) of voxelotor and the patient has stable hemoglobin levels?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
4. Is the request for a renewal of crizanlizumab?	**Yes**: Go to #5	**No:** Go to #6
5. Has the patient demonstrated improvements in pain symptoms from baseline since starting crizanlizumab treatment?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the request for a renewal of L-glutamine (ENDARI)?	**Yes:** Go to #7	**No:** See above for initial approval criteria.

Renewal Criteria		
7. Has the patient demonstrated improvements in pain symptoms from baseline since starting L-glutamine treatment?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 4//22 (KS), 6/20 (KS)
Implementation: 5/1/22; 7/1/20