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Drug Class Review with New Drug Evaluations: Sickle Cell Disease

Date of Review: June 2020
Generic Name: crizanlizumab
voxelotor

End Date of Literature Search: 02/14/2020
Brand Name (Manufacturer): Adakveo® (Novartis)
Oxbryta™ (Global Blood Therapeutics)

Purpose for Class Review: The purpose of this update is to review drug therapy evidence for the treatment of sickle cell disease (SCD) and create a preferred drug list (PDL) class for this disease. Additionally, there are 2 new drugs that will be reviewed to determine place in therapy for SCD.

Research Questions:

1. Is there high-quality comparative evidence demonstrating efficacy or effectiveness for therapies used for SCD?
2. Is there evidence for harms data for the therapies used for SCD?
3. Are there subgroups of patients based on demographics (e.g., age, race, sex, socioeconomic factors) in which one therapy for SCD would be more effective or associated with less harm?
4. What is the evidence for efficacy and harms associated with voxelotor and how does this compare to other treatments for SCD?
5. What is the evidence for efficacy and harms associated with crizanlizumab and how does this compare to other treatments for SCD?

Conclusions:

- Two clinical practice guidelines, one systematic review and 3 randomized controlled trials were identified that met inclusion criteria. Evidence from these sources revealed a paucity of high-quality evidence and limited treatment options for SCD.
- Hydroxyurea is appropriate for patients with SCD who experience pain crises 3 or more times in a 12-month period, and for infants 9-42 months of age, children, and adolescents to prevent complications of SCD (pain crisis frequency, duration, intensity, hospital admissions, vaso-occlusive crisis and opioid use) based on high-quality evidence.[1] Hydroxyurea should also be considered in adult patients who have sickle cell-related pain or sickle cell anemia that interferes with daily activities or quality of life and for patients with severe or recurrent acute coronary syndrome (moderate quality of evidence). These recommendations were reiterated in a clinical practice guideline by the National Heart, Lung and Blood Institute.[2]
- There is low quality of evidence from one trial of 230 patients that glutamine powder reduced the median number of pain crises more than placebo, with or without concomitant hydroxyurea therapy, median of 3 versus 4 over 48 weeks, respectively (P=0.005).[3]
- There is low quality of evidence from a small, double-blind, phase 3, randomized controlled trial lasting 72 weeks that more patients with SCD taking voxelotor had a hemoglobin response (defined by the investigators as an increase of more than 1.0 g/dL from baseline at week 24) compared to placebo.[4] There is insufficient evidence on the clinically meaningful change of hemoglobin levels. Patients on voxelotor 900 mg orally daily reported a 26% absolute increased response over placebo (NNT=4) and voxelotor 1500 mg orally daily had a 44% absolute increased response over placebo (NNT=3).[4] No statistically

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significant difference in annualized rate of vaso-occlusive events was found between either dose of voxelotor and placebo. Voxelotor was approved by the Food and Drug Administration (FDA) via an accelerated approval process. Additional evidence of clinical benefit is required by the FDA.

- There is low quality evidence from one phase 2 trial lasting 52 weeks that crizanlizumab 5 mg/kg intravenously (IV) reduced the annual number of pain crises in patients with SCD more than placebo by 1.35 less attacks per year (1.63 vs. 2.98; (95% confidence intervals not reported; P=0.01).[5]

Recommendations:

- Designate drugs for SCD as a PDL class.
- Add a hydroxyurea formulation as a preferred treatment option on the PDL.
- Designate voxelotor, crizanlizumab, l-glutamine (ENDARI), hydroxyurea capsules and tablets (DROXIA, HYDREA and SIKLOS) as non-preferred.
- Evaluate drug costs in the executive session.
- After executive session hydroxyurea capsules were made preferred and the above recommendations were approved as non-preferred products.

Background:

Sickle cell disease is a common genetic disorder, with an estimated incidence of about 100,000 people in the United States (US).[6] Sickle cell disease is most prevalent in people of African, Mediterranean and Asian descent.[6] Sickle cell disease often presents in toddlers or young children and results in shortened life expectancy.[7] The cause of SCD is a genetic mutation of the hemoglobin structure that results in red blood cells with a sickle-shape which are inflexible and have increased the viscosity of blood.[8] Patients with SCD may either inherit two sickle genes (HbSS genotype) or inherit one sickle cell gene from one parent and different hemoglobin gene from the other parent (e.g., hemoglobin C, ß-thalassemia).[1] The HbSS genotype is the most common genotype, occurring in 60-75% of SCD patients in the US.[9] Both the HbSS and HbSß-thalassemia genotypes are referred to as sickle cell anemia (SCA).[2] Common characteristics of SCD are red blood cell hemolysis and vaso-occlusion, obstruction of blood flow. The blockage of small blood vessels prevents oxygen delivery to tissues causing severe pain.[1] Resulting comorbidities include blood clots, infection, organ damage, retinopathy, stroke and pain in the joint, extremities, back or chest.

Standard pharmacological treatment options for SCD are hydroxyurea, l-glutamine, and most recently, crizanlizumab and voxelotor. Hydroxyurea is the most utilized treatment for SCD and works by increasing fetal hemoglobin (HbF) concentrations. Infants are born with high levels of HbF, which gradually decreases with age to a normal adult level of HbF of less than 1% by age 2.[10] Studies have found that increasing levels of HbF help to prevent disorders of beta globin gene expression associated with SCD.[10] By increasing HbF concentrations, hydroxyurea has been found to increase nitric oxide metabolism (which is important in the synthesis of HbF) and reduction in red cell-endothelial interaction and erythrocyte density.[1] Improvement in these measures is associated with reduced pain crises (approximately 2.8 less pain crises annually compared to placebo), blood transfusions, and hospital admissions; however, there is no evidence that hydroxyurea improves mortality.[1] It is recommended to monitor blood counts for reduction in neutrophils and platelet in patients taking hydroxyurea. Hydroxyurea therapy has also been associated with teratogenic effects and reduced male fertility.[1] Glutamine was approved in 2017 for reduction in acute complications of SCD in adults and pediatric patients, 5 years of age and older.[11] While the exact mechanism of glutamine is unknown, it is thought to prevent oxidative damage to red blood cells, which are more susceptible in patients with SCD.[11] Non-pharmacological therapies for SCD include blood transfusions (to increase the oxygen capacity of blood), hemopoietic stem cell transplant and phlebotomy. Phlebotomy aids in reduction of HbS polymerization associated with SCD and subsequently decreases hospitalization duration and reduced Hb levels.[12]

Clinically meaningful outcomes for SCD include reduction in stroke, sickle cell pain crises, need for blood transfusion, end-organ damage, and mortality. Increases in hemoglobin concentrations are often measured, with increases associated with medication efficacy; however, specific HbF concentrations have not been correlated with subsequent outcome changes.[7]

Drug utilization in this class is very low and accounts for minimal expenditures. In 2019, 15 Oregon Health Plan fee-for-service patients had a diagnosis of SCD.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 1. Indications and Dosing.

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Crizanlizumab Adakveo®[13] (Novartis)	Reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease	10 mg/mL solution via intravenous infusion	5 mg/kg over a period of 30 minutes on Week 0, Week 2 and every 4 weeks thereafter
Hydroxyurea Droxia® and Siklos®[14,15] (Bristol-Myers Squibb and Addmedica)	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	200 mg, 300 mg and 400 mg capsules orally	15 mg/kg/day as a single daily dose for initial 12 weeks. Dose may be increased by 5mg/kg/day every 12 weeks until maximum tolerated dose or 35 mg/kg/day is reached
L-glutamine Endari™[11] (Emmaus Medical)	Reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	5 grams powder per packet orally in 8 oz. beverage or 4 oz. of food	5 grams to 15 grams twice daily based on body weight
Voxelotor Oxbryta™[16] (Global Blood Therapeutics)	Treatment of sickle cell disease in adults and pediatric patients 12 years of age and older	500 mg tablets orally	1500 mg once daily

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. The Medline search strategy used for this review is available in **Appendix 2**, 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 clinical practice guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

Cochrane – Hydroxyurea for Sickle Cell Disease

A 2017 Cochrane systematic review evaluated randomized and quasi-randomized controlled trials of hydroxyurea lasting at least one month.[1] Sixteen trials in children and adults with hemoglobin SS (HbSS), hemoglobin SC (HbSC), or hemoglobin Sß^{0}thalassemia (HbSß^{0}thal) genotypes were identified. Most trials lasted 6-24 months.

Placebo-controlled comparisons provide moderate quality evidence that hydroxyurea decreases pain alteration (pain crisis frequency, duration, intensity, hospital admissions, vaso-occlusive crisis and opioid use) more than placebo (results were not pooled due to different measures of pain alterations).[1] Moderate evidence also suggests a decrease in life-threatening illnesses (acute chest syndrome and transfusions) in patients treated with hydroxyurea compared to placebo (results not pooled). However, risk of death was not statistically significantly different between hydroxyurea and placebo based on moderate evidence (RR 0.39; 95% CI, 0.08 to 1.96).[1] Fetal hemoglobin was increased in patients taking hydroxyurea compared to placebo (results not pooled). There was low quality evidence that hydroxyurea decreased pain recall more than placebo (MD 0.70; 95% CI, 0.11 to 1.29; P=0.02). Patients taking hydroxyurea reported a significant reduction in absolute neutrophil count compared to placebo (moderate evidence). Adverse events were similar between groups.

Hydroxyurea/phlebotomy was compared to transfusion/chelation in children and adults with increased risk of stroke (HbSS and HbSß^{0}thal).[1] Phlebotomy aids in decreasing the viscosity of blood by reducing Hb levels and mean corpuscular Hb concentrations. The result of Hb reductions is reduced HbS polymerization, which is elevated in SCD.[12] There was moderate evidence of no difference between groups in the incidence of life-threatening illness (neurological events, hepatobiliary disease, or splenic sequestration); however, there were more acute chest syndrome, infections and parasite infestations in the hydroxyurea/phlebotomy group compared to transfusion/chelation. There was an increase in fetal hemoglobin in patients treated with hydroxyurea/phlebotomy compared to transfusion/chelation based on moderate evidence (results not pooled) and a decrease in absolute neutrophil count in patients treated with hydroxyurea/phlebotomy compared to transfusion/chelation.[1]

In conclusion, hydroxyurea was effective in children and adults for the outcome of pain and acute complications. The risk of life-threatening neurologic events was reduced in patients given hydroxyurea. Additional long-term data and the effect of hydroxyurea on fertility and reproduction are needed.

After review, 9 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[8,17–24]

Guidelines:

National Heart, Lung and Blood Institute (NHLBI) – Evidence-Based Management of Sickle Cell Disease

In 2014, the NHLBI updated the guidelines on management of SCD.[2] The guidelines were supported by a systematic review of the literature, determining the quality of the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) and formulating recommendations ranging from "weak" to "strong".[2] Hydroxyurea was the only available therapy for SCD at the time the guidelines were published. Recommendations for the use of hydroxyurea in SCD are presented in **Table 2**. Guidelines recommend the use of a prescribing monitoring protocol to be used in patients taking hydroxyurea, including blood counts and metabolic monitoring.

Table 2. NHLBI Recommendations for the Use of Hydroxyurea in Patients with Sickle Cell Disease[2]

Recommendation	Level of Evidence
1. Adults with SCA who have 3 or more sickle-cell moderate to severe pain crises in a 12-month period should be treated with hydroxyurea	Strong Recommendation, High-Quality of Evidence
2. Hydroxyurea should be given to adults with SCA who have sickle-cell associated pain that interferes with daily activities and quality of life	Strong Recommendation, Moderate-Quality of Evidence
3. Adults with SCA who have a history of severe and/or recurrent ACS, treat with hydroxyurea	Strong Recommendation, Moderate-Quality of Evidence
4. Hydroxyurea should be used as a treatment in adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life	Strong Recommendation, Moderate-Quality of Evidence
5. Infants (9 months of age and older), children and adolescents with SCA should be offered hydroxyurea regardless of clinical severity to minimize complications of SCD	Strong Recommendation, High-Quality of Evidence for ages 9-42 months Moderate Recommendation, Moderate-Quality of Evidence for children >42 months and adolescents
6. Hydroxyurea can be given to adults and children with SCD who have chronic kidney disease and are taking erythropoietin to improve anemia	Weak Recommendation, Low-Quality of Evidence
7. Hydroxyurea should be discontinued in women who are pregnant or breastfeeding	Moderate Recommendation, Low-Quality of Evidence

Abbreviations: ACS = acute coronary syndrome; SCA = sickle cell anemia; SCD = sickle cell disease

American Society of Hematology – Cardiopulmonary and Kidney Disease 2019 Guidelines for Patients with Sickle Cell Disease

The American Society of Hematology updated its guidance in 2019 for patients with cardiopulmonary and renal complications related to SCD.[25] The evidence was evaluated using GRADE methodology and incorporated into recommendations. Sickle cell pharmacotherapy recommendations included only for the use of combination hydroxyurea and erythropoiesis-stimulating agents, up to a hemoglobin threshold of 10 g/dL, for children and adults with worsening anemia associated with chronic kidney disease (very low quality evidence).[25]

Additional Guidelines for Clinical Context:

After review, two guidelines were excluded due to poor quality.[26,27]

Randomized Controlled Trials:

A total of 234 citations were manually reviewed from the initial literature search. After further review, 233 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Niihara, et al.[3] (n=230)	L-glutamine 0.3 g/kg orally twice daily Vs. Placebo 48 weeks	Patients aged 5-58 years with SCA (HbSS or HbS ß^0-thalassemia) +/- stable dose of hydroxyurea and h/o ≥2 pain crises in previous year	Incidence of pain crises among patients at 48 weeks	L-glutamine: 3.0 (median) (CI not reported) Placebo: 4.0 (median) (CI not reported) P=0.005 *L-glutamine reduced the number of pain crises more than placebo*

Abbreviations: HbS ß^0-thalassemia = sickle ß^0-thalassemia; HbSS = homozygous hemoglobin S; h/o = history of; SCA = sickle cell anemia; SCD = sickle cell disease

NEW DRUG EVALUATION: Voxelotor (Oxbryta™)

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Voxelotor is a deoxygenated sickle hemoglobin (HbS) polymerization inhibitor which binds to hemoglobin to stabilize the oxygen state.[16] HbS polymerizes when deoxygenated which results in membrane damage and red-cell sickling. Voxelotor was approved via the accelerated approval pathway for the treatment of SCD in adult and pediatric patients 12 years of age and older.[4] Due to the accelerated approval, post-marketing studies to evaluate clinical benefit are required for voxelotor.

The HOPE trial was a phase 3, double-blind, placebo-controlled, 24-week, randomized trial used for the approval of voxelotor (see **Table 5**).[4] Patients were a median age of 25 years, 67% were African-American, predominately with HbSS genotype, and 65% were taking hydroxyurea.[4] Voxelotor 900 mg or 1500 mg once daily was compared to placebo in adults with sickle cell anemia (HbSS, sickle hemoglobin C disease or HbSß^{0}thal). The primary endpoint was the percentage of patients who had a hemoglobin response (an increase of more than 1.0 g/dL from baseline) at week 24.[4]

Voxelotor demonstrated efficacy over placebo for both doses. Thirty-three percent of patients who received voxelotor 900 mg had a hemoglobin response compared to 51% who received voxelotor 1500 mg and 7% for the placebo group.[4] The absolute change compared to placebo was 26% for voxelotor 900 mg (NNT of 4) and 44% for voxelotor 1500 mg (NNT 3).[4] Attrition rates were 21-27% with voxelotor and 27% in patients treated with placebo.[7] There was no decrease in annualized vaso-occlusive events between groups.

Voxelotor was only studied in a small group of patients for a short duration. Only the surrogate endpoint of hemoglobin concentration was found to be significantly increased over placebo while a clinical endpoint of vaso-occlusive events was no different between groups. Additionally, most patients also received

hydroxyurea which could also have a positive effect on hemoglobin concentrations. This study was also funded by the manufacturer. Additional evidence to demonstrate long-term efficacy and clinical benefit in health outcomes is warranted. An efficacy trial involving the use of voxelotor in children with SCD is currently being conducted.

Clinical Safety:
The most common adverse events experienced amongst trial participants were headache, diarrhea, abdominal pain, nausea, rash, fatigue and pyrexia.[7] Serious drug adverse reactions were rare. Serious adverse events and adverse events related to discontinuation were similar between groups.[4]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Stroke reduction
2) Reduction in vaso-occlusive crisis
3) Reduction in pain symptoms
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Hemoglobin response

Table 4. Pharmacology and Pharmacokinetic Properties.[16]

Parameter	
Mechanism of Action	Sickle hemoglobin polymerization inhibitor which prevents deoxygenation of hemoglobin (deoxygenated hemoglobin polymerizes and results in red-cell sickling and membrane damage)
Oral Bioavailability	Not described
Distribution and Protein Binding	338 L and Protein binding is 99.8%
Elimination	62.6% in the feces and 35.5% in the urine
Half-Life	35.5 hours
Metabolism	CYP3A4

Abbreviations: HbS = deoxygenated sickle hemoglobin

Table 5. Voxelotor Comparative Evidence Table.

Ref./ Study Design	**Drug Regimens/ Duration**	**Patient Population**	**N**	**Efficacy Endpoints**	**ARR/NNT**	**Safety Outcomes**	**ARR/NNH**	**Risk of Bias/ Applicability**
1. Vichinsky, et al.[4] (HOPE)	1. Voxelotor 900 mg PO once daily 2. Voxelotor 1500 mg PO once daily	Demographics: Median Age: 25 y Female: 58% Concomitant hydroxyurea: 65%	ITT: 1. 92 2. 90 3. 92	Primary Endpoint: % with Hgb response at week 24* 1. 30 (33%) (95% CI, 23 to 42) 2. 46 (51%) (95% CI, 41 to 61) 3. 6 (7%) (95% CI, 1 to 12)		Serious Adverse events: 1. 16 (17.4%) 2. 17 (19.3%) 3. 15 (16.5%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients were assigned in a 1:1:1 ratio. There were approximately 10% more women in the voxelotor 1500 mg group.

MC, PC, PG, DB, Phase 3, RCT	3. Placebo N = 274 Screening period: 28-35 days Treatment period: 72 weeks (median follow-up of 39 weeks)	Baseline Hgb: 8.5 mg/dL Patients with 1 vaso-occlusive crisis in the past 12 months: 42% Patients with 2-10 vaso-occlusive crises in the past 12 months: 58% HbSS genotype: 75% Key Inclusion Criteria: - Age 12-65 years - SCD diagnosis (homozygous Hgb S or Hgb Sß-thalassemia) - Hgb 5.5 - 10.5 g/dL - 1-10 vaso-occlusive crises in past 12 months Key Exclusion Criteria: - Pregnant/ breastfeeding - Regular RBC transfusions - Hospitalization for sickle cell crisis or other vaso-occlusive event within 14 days - Hepatic dysfunction or severe renal dysfunction - Active infection - Cancer	PP: 1. 73 2. 66 3. 73 Attrition: 1. 19 (21%) 2. 24 (27%) 3. 19 (26%)	P<0.001 for both voxelotor doses vs. placebo Secondary Endpoints: Change in Hgb from baseline to week 24: 1. 0.6 g/dL (95% CI, 0.3 to 0.8) 2. 1.1 g/dL (95% CI, 0.9 to 1.4) 3. -0.1 g/dL (95% CI, -0.3 to 0.2) Voxelotor 900 mg vs. placebo: P<0.05 Voxelotor 1500 mg vs. placebo: P<0.001	26%/ 4 44%/ 3 NA NA	Withdrawals due to Adverse Events: 1. 5 (5.4%) 2. 8 (9.1%) 3. 4 (4.4%) Vaso-occlusive crisis (% not applicable): 1. 183 2. 179 3. 219 Headache: 1. 14 (15%) 2. 23 (26%) 3. 20 (22%)		Performance Bias: Low. Products were identical, preserving blinding. Blinding of participants and personnel were blinded. Detection Bias: Unclear. Details on data analysis and maintaining blinding was not described. Attrition Bias: High. Attrition 21-27%, with last observation carried forward imputation. Reporting Bias: Low. Outcomes were reported as stated. Other Bias: High. Funded by manufacturer. **Applicability**: Patient: The majority of the included patients had a history of more than one vaso-occlusive crises in the last year and those with the HbSS genotype. Intervention: Voxelotor dose appropriate based on phase 2 trials. Comparator: Placebo appropriate to establish efficacy of voxelotor. Outcomes: Hemoglobin concentrations are a surrogate outcome and clinically significant changes have not been determined. The clinical significance of a 1 g/dL is unknown. Setting: 60 centers in 12 countries (North America, Europe or other).

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; d = days; DB = double-blind; Hgb = hemoglobin; ITT = intention to treat; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; PC = placebo controlled; PG = parallel group; PO = orally; PP = per protocol; RBC = red blood cell; RCT = randomized controlled trial; SCD = sickle cell disease; y = year.
Key: * Hemoglobin response was defined as increase of more than 1.0 g/dL from baseline at week 24

NEW DRUG EVALUATION: Crizanlizumab

See **Appendix 4** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Crizanlizumab is a selectin blocker, a monoclonal antibody that binds to P-selectin. Up-regulation of P-selectin in endothelial cells and platelets are associated with cell interactions involved in vaso-occlusion and sickle cell pain crises. Crizanlizumab was approved, under the Breakthrough Therapy Designation, to reduce the frequency of vaso-occlusive crises n adult and pediatric patients, ages 16 and older, with SCD.[13] Crizanlizumab is given by IV infusion over 30 minutes at week 0, week 2 and every 4 weeks thereafter. Approval was based on one phase 2 study (SUSTAIN) (See **Table 7**).[5]

The SUSTAIN trial was a double-blind, placebo-controlled, randomized clinical trial that evaluated crizanlizumab 2.5 mg/kg and 5 mg/kg versus placebo and given IV 14 times over 52 weeks.[5] A loading dose of 2 doses of crizanlizumab or placebo were given 2 weeks apart and then one dose every 4 weeks. The median age in the study was 28 years, 55% were female, and 71% had the HbSS genotype. The primary endpoint was the annualized rate of sickle cell-related pain crises (total number of crises multiplied by 365 and divided by [end date – date of randomization + 1]. A sickle cell pain crisis event was a pain episode due to a vaso-occlusive event requiring treatment with opioids or nonsteroidal anti-inflammatory drugs. Additional crisis events included in the primary endpoint were acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism; however, there were no events in any of the groups. Crizanlizumab 5 mg/kg was more effective in reducing the annualized rate of sickle cell pain crises compared to placebo (1.63 (95% CI, 0.0 to 3.97) vs. 2.98 (95% CI, 1.25 to 5.87); P=0.01).[5] Crizanlizumab 2.5 mg/kg was not statistically different from placebo in pain crises reduction. Reduction sickle cell -related pain crises was demonstrated in patients on the 5 mg/kg dose irrespective of hydroxyurea use or genotype.[9]

Attrition was high in all groups (32-37%) in the trial. The most common reason in all groups was withdrawal by subject. Multiple imputation was performed for dropouts using data from those patients who completed the study. Efficacy beyond 52 weeks has not been studied.

Clinical Safety:

Adverse events that occurred in more than 3% of patients who received crizanlizumab versus placebo were nausea, arthralgia, back pain and pyrexia.[13] Serious adverse reactions occurred in 2 patients treated with crizanlizumab. Discontinuations due to adverse events occurred in 2.7% of crizanlizumab-treated patients compared to 5% of placebo treated patients.[9] There were no detectable antibody responses against crizanlizumab reported.[5]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Stroke reduction
2) Reduction in vaso-occlusive crisis
3) Reduction in pain symptoms
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Annual rate of sickle cell pain crisis

Table 6. Pharmacology and Pharmacokinetic Properties.

Parameter	
Mechanism of Action	Humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1.
Oral Bioavailability	Not applicable
Distribution and Protein Binding	4.26 L and Protein binding not described
Elimination	Not described
Half-Life	7.6 days
Metabolism	Expected to be metabolized into small peptides by catabolic pathways.

Table 7. Crizanlizumab Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Ataga, et al.[5] (SUSTAIN) MC, PC, DB, Phase 2, RCT	1. Crizanlizumab 2.5 mg/kg IV 2. Crizanlizumab 5 mg/kg IV 3. Placebo IV All treatments given 14 times over 52 weeks	Demographics: Median Age: 28 y Female 55% Concomitant hydroxyurea: 63% Baseline HbSS Genotype: 71% Patients with a history of 2-4 pain crises in the previous 12 months at baseline: 63% Key Inclusion Criteria: - Ages 16-65 years - sickle cell diagnosis (homozygous hgb S or hgb Sß^0-thalassemia, sickle	ITT: 1. 66 2. 67 3. 65 PP: 1. 45 2. 43 3. 41 Attrition: 1. 21 (32%) 2. 24 (36%) 3. 24 (37%)	Primary Endpoint: Annual rate of sickle cell pain crisis: 1. 2.01 (95% CI, 1.00 to 3.98) 2. 1.63 (95% CI, 0.00 to 3.97) 3. 2.98 (95% CI, 1.25 to 5.87) Crizanlizumab 2.5 mg vs. placebo: TD -32.6% P=0.18 Crizanlizumab 5.0 mg vs. placebo: TD -45.3% P=0.01 Secondary Endpoints: Annual rate of days hospitalized:	NS NA	Serious Adverse Events: 1. 21 (33%) 2. 17 (26%) 3. 17 (27%) Pyrexia: 1. 0 2. 2 (3%) 3. 1 (2%) Headache: 1. 14 (22%) 2. 11 (17%) 3. 10 (16%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 centrally based on a block design with stratification based on number of pain crises in the preceding year and concomitant hydroxyurea use. Baseline characteristics were similar. Performance Bias: Low. Same administration to mask treatments. Compounding pharmacist was unblinded. All other sponsor and study contacts were blinded. Detection Bias: Low. Crises review committee, used for analysis of primary endpoint, was comprised of 3 independent hematologists. Attrition Bias: High. Attrition was high in all groups. Missing data will be imputed as the maximum rate of crises among study patients. Reporting Bias: Low. Outcome were reported as outlined. Other Bias: High. Study was funded by the manufacturer

		hgb C disease, hgb Sß+-thalassemia or other genotypes) - 2-10 sickle cell-related pain crises in past 12 months - hydroxyurea use past 6 months; stable dose for at least 3 months Key Exclusion Criteria: - Long-term red-cell transfusion therapy - Hgb <4.0 g/dL - cancer - Stroke in past 2 y		1. 6.87 (95% CI, 0.00 to 18.00) 2. 4.00 (95% CI, 0.00 to 25.72) 3. 6.87 (95% CI, 0.00 to 28.30) Crizanlizumab 2.5 mg vs. placebo P=0.84 Crizanlizumab 5.0 mg vs. placebo P=0.45				**Applicability**: Patient: The annual crisis rate was reduced by 34.6% in patients with the HbSS genotype and 50.5% with other genotypes, demonstrating effectiveness in both populations. Ninety-two percent of patients were African American with low applicability to other populations. Intervention: Comparisons of two doses of crizanlizumab was appropriate based on a phase 1 trial. Comparator: Placebo comparison appropriate for a phase 2 study in order to establish efficacy of drug. Outcomes: Sickle cell pain crisis is a clinically meaningful endpoint. Actual number of pain crises would be helpful. Setting: Sixty sites in 3 countries (151 patients from US sites).

Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = double-blind; HgB = hemoglobin; HbSS = homozygous hemoglobin S; ITT = intention to treat; IV = intravenous; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; PC = placebo controlled; PP = per protocol; TD = treatment difference; y = years

References:

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Appendix 1: Specific Drug Information

Table 8. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics (mean)
Crizanlizumab[13]	Humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1.	NA	Expected to be metabolized into small peptides by catabolic pathways.	• Half-life: 7.6 days • Cmax: 0.16 mg/mL • AUC_{last}*: 33.6. mg/hr/mL • Vd: 4.26 L
Hydroxyurea[14,28]	Exact mechanism unknown. Thought to inhibit DNA synthesis by acting as a	≥ 80%	60% hepatic metabolism and a minor pathway of degradation by urease found	• Half-life: 1.7 hours (pediatrics) and 1.9-3.9 hours (adults) • Cmax: NA

	ribonucleotide reductase inhibitor.		in intestinal bacteria. Urinary excretion accounted for 40%.	• AUC: NA • Vd: 12 L (pediatrics) and 20 L (adults)
L-glutamine[11]	Exact mechanism unknown. L-glutamine may improve the NAD (the pyridine nucelotides) redox potential in sickle RBCs through increasing availability of reduced glutathione and reducing damage in red blood cells.	NA	Various metabolic activities, including formation of glutamate and synthesis of proteins, nucleotides and amino sugars.	• Half-life: 1 hour • Cmax: NA • AUC: NA • Vd: 200 mL/kg
Voxelotor[16]	Hemoglobin S (HbS) polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs.	Peak concentrations occur 6-18 hours after oral administration.	Metabolism is via Phase I (oxidation and reduction), Phase II (glucuronidation) and combination of Phase I and Phase II metabolism; primarily by CYP3A4.	• Half-life: 35.5 hours • Cmax: 12.6 mcg/mL • AUC: 246 mcg·hr/mL • Vd: 338 L

Abbreviations: AUC = area under the curve; Cmax = maximum concentration; NA – not available; RBCs = red blood cells; Vd = volume of distribution
Key: * AUC_{last} – the last measurement recorded

Use in Specific Populations:

- Crizanlizumab is approved for use in pediatric patients 16 years of age and older. Use in pregnant women and geriatric patients is insufficient.
- Glutamine is safe and effective for use in pediatric patients 5 years and older. There is limited data for use in geriatric patients but some evidence suggests a similar response as in younger individuals.
- Hydroxyurea has not been studied in pediatrics. Use in pregnant females is limited. A lower dose may be required for geriatric patients and renal function should be monitored, as risk of adverse events may be increased with impaired renal function.
- Voxelotor has been studied as safe and effective in pediatrics 12 years and older. There is insufficient evidence for use in geriatric patients and pregnant women.

Drug Safety:

Boxed Warnings: Droxia (hydroxyurea) capsules have a boxed warning for the risk of severe myelosuppression. Avoid use in patients with decreased bone marrow function. Cancer has also been reported in patients taking hydroxyurea and sun protection is advised.

Risk Evaluation Mitigation Strategy Programs: Not applicable.

Contraindications: There are no contraindications reported with glutamine or crizanlizumab. Voxelotor and hydroxyurea should not be used in patients with hypersensitivity to it or excipients.

Table 9. Summary of Warnings and Precautions.

Warning/Precaution	Crizanlizumab-tmca	Hydroxyurea	L-glutamine*	Voxelotor
Infusion-related reactions	X			
Interference with automated platelet counts	X			
Hypersensitivity Reactions				X
Interference with measurement of Hb subtypes				X
Myelosuppression		X		
Malignancies		X		
Embryo-fetal toxicity		X		
Vasculitic toxicity		X		
Avoid live vaccinations		X		
Avoid concomitant use of antiretroviral drugs		X		
Skin erythema in patients recently receiving radiation		X		

Key: * No contraindications or precautions

Appendix 2: Trial Abstracts

A Phase 3 Trial of l-Glutamine in Sickle Cell Disease

Yutaka Niihara , Scott T Miller , Julie Kanter , Sophie Lanzkron , Wally R Smith , Lewis L Hsu , Victor R Gordeuk , Kusum Viswanathan , Sharada Sarnaik , Ifeyinwa Osunkwo , Edouard Guillaume , Swayam Sadanandan , Lance Sieger , Joseph L Lasky , Eduard H Panosyan , Osbourne A Blake , Tamara N New , Rita Bellevue , Lan T Tran , Rafael L Razon , Charles W Stark , Lynne D Neumayr , Elliott P Vichinsky , Investigators of the Phase 3 Trial of l-Glutamine in Sickle Cell Disease

Background: Oxidative stress contributes to the complex pathophysiology of sickle cell disease. Oral therapy with pharmaceutical-grade l-glutamine (USAN, glutamine) has been shown to increase the proportion of the reduced form of nicotinamide adenine dinucleotides in sickle cell erythrocytes, which probably reduces oxidative stress and could result in fewer episodes of sickle cell-related pain.

Methods: In a multicenter, randomized, placebo-controlled, double-blind, phase 3 trial, we tested the efficacy of pharmaceutical-grade l-glutamine (0.3 g per kilogram of body weight per dose) administered twice daily by mouth, as compared with placebo, in reducing the incidence of pain crises among patients with sickle cell anemia or sickle β^0-thalassemia and a history of two or more pain crises during the previous year. Patients who were receiving hydroxyurea at a dose that had been stable for at least 3 months before screening continued that therapy through the 48-week treatment period.

Results: A total of 230 patients (age range, 5 to 58 years; 53.9% female) were randomly assigned, in a 2:1 ratio, to receive l-glutamine (152 patients) or placebo (78 patients). The patients in the l-glutamine group had significantly fewer pain crises than those in the placebo group (P=0.005), with a median of 3.0 in the l-glutamine group and 4.0 in the placebo group. Fewer hospitalizations occurred in the l-glutamine group than in the placebo group (P=0.005), with a median of 2.0 in the l-glutamine group and 3.0 in the placebo group. Two thirds of the patients in both trial groups received concomitant hydroxyurea. Low-grade nausea, noncardiac chest pain, fatigue, and musculoskeletal pain occurred more frequently in the l-glutamine group than in the placebo group.

Conclusions: Among children and adults with sickle cell anemia, the median number of pain crises over 48 weeks was lower among those who received oral therapy with l-glutamine, administered alone or with hydroxyurea, than among those who received placebo, with or without hydroxyurea. (Funded by Emmaus Medical; ClinicalTrials.gov number, NCT01179217 .).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to January 24, 2020

Search Strategy:

#	Searches	Results
1	hydroxyurea.mp. or Hydroxyurea/	12022
2	crizanlizumab.mp.	19
3	l-glutamine.mp. or Glutamine/	18572
4	voxelotor.mp.	16
5	1 or 2 or 3 or 4	30594
6	limit 5 to (english language and humans and yr="2000 -Current")	8461
7	limit 6 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	234

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, vasoocclusive crisis, hospitalizations, pain scores
Timing	Symptom onset
Setting	Outpatient

Sickle Cell Anemia Drugs

Goal(s):

- Approve the use of drugs for sickle cell disease in a cost-effective manner based on evidence.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred drugs

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

Approval Criteria		
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a PA. • Preferred products are evidence-based 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. Is the patient taking hydroxyurea, failed treatment (stable dose for at least 3 months) or have contraindications to hydroxyurea treatment?	**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 12 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 AND have a history of at least 1 pain crisis in the last 12 months?	**Yes:** Approve for up to 6 months. Record baseline hemoglobin value.	**No:** Pass to RPh. Deny; medical appropriateness
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 renewal of voxelotor?	**Yes**: Go to #2	**No:** Go to #3
2. Has the patient had an increase in hemoglobin of at least 1 g/dL from baseline hemoglobin level since starting voxelotor?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is the request for a renewal of crizanlizumab?	**Yes**: Go to #4	**No:** Go to #5
4. Has the patient had a reduction in annual pain crises by at least 45%?	**Yes:** Approve for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness.
5. Is the request for a renewal of L-glutamine (ENDARI)?	Yes: Go to #6	No: See above for initial approval criteria.
6. Has the patient has a reduction in annual pain crises of a least 1 in the last 12 months?	Yes: Approve for up to 12 months.	No: Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 6/20 (KS)
Implementation:7/1/20