Therapeutic Class Overview
Sickle cell anemia agents

INTRODUCTION

- Sickle cell disease (SCD) is a group of inherited red blood cell (RBC) disorders. The group of disorders comprising SCD is caused by a single mutation of the gene that codes for hemoglobin S (HbS), which substantially impacts the stability of the hemoglobin molecule and each RBC as a whole, as they form a sickle shape. Due to the mutation, the hemoglobin becomes more coagulable in its normal environment and cells are poor carriers of oxygen. The most common SCD genotypes include homozygous hemoglobin SS (HbSS, referred to as sickle cell anemia [SCA]) and HbS β^0-thalassemia; these genotypes are clinically similar and are associated with the most severe clinical manifestations *(National Institutes of Health [NIH] 2014, Vichinsky & Mahoney 2018)*.
- Vaso-occlusive phenomena (eg, vaso-occlusive crises [VOCs] or vaso-occlusive events [VCEs]) and hemolysis are the major clinical features of SCD (*Field & Vichinsky 2018*). Vaso-occlusion results in recurrent pain episodes (also termed sickle cell crises [SCCs]) and various organ system complications including serious infection, acute chest syndrome (ACS), renal failure, hepatobiliary complications, anemia, cerebrovascular and cardiovascular events, priapism, ocular disorders, neuropathy, and splenic sequestration that can lead to lifelong disabilities and death (*Food and Drug Administration [FDA] Multidiscipline Review [OXBRYTA] 2018, Vichinsky & Mahoney 2018*). VOC pain episodes are the most frequent cause of recurrent morbidity in SCD and account for the majority of SCD-related hospitalizations (*FDA Multidiscipline Review [ADAKVEO] 2018*).
- The hemoglobin level in patients with SCD is also a measure that reflects the severity and clinical course of the disease. Patients with lower hemoglobin levels (ie, anemia or hemolytic anemia) tend to have an increased risk for end-organ complications (ie, chronic kidney disease, pulmonary hypertension, stroke, and silent cerebral infarctions), and early mortality (*FDA Multidiscipline Review [OXBRYTA] 2018*). Patients may require RBC transfusions to increase hemoglobin levels.
- The exact number of people with SCD in the United States (U.S.) is unknown; it is estimated that SCD affects 100,000 Americans (*Centers for Disease Control and Prevention [CDC] Web site)*. Most of those affected are of African ancestry or self-identify as Black (*NIH 2014*). Although SCD is associated with major morbidity, currently, more than 90% of children with SCD in the U.S. and the United Kingdom survive into adulthood; however, their lifespans remain shortened by 2 or 3 decades compared to the general population.
- Hematopoietic stem cell transplantation (HSCT) and gene therapy are the only curative options for SCD; however, only a small percentage of patients are eligible for these treatment options (*FDA Multidiscipline Review [OXBRYTA] 2018*).
- Treatment options for SCD are different for each patient and depend on the symptoms *(Field & Vichinsky 2018*). In addition to lifelong supportive care (eg, RBC transfusions, pain management strategies, vaccinations, antibiotic prophylaxis) or treatment during an acute VOC (eg, pain management with non-steroidal anti-inflammatories [NSAIDs] or opioids, intravenous (IV) fluids, supplemental oxygen), patients may be placed on disease-modifying agents (*FDA Multidiscipline Review [OXBRYTA] 2018*). Currently, hydroxyurea (Droxia, Siklos, or Hydrea) is the only guideline-recommended agent for treatment of SCD (*NIH 2014*). However, L-glutamine (Endari) received FDA approval for the treatment of SCD in July, 2017. Two new agents were also recently FDA-approved for the treatment of SCD:
  - Crizanlizumab-tmca is the first targeted therapy approved for SCD, specifically inhibiting selectin (*FDA Press Release [crizanlizumab-tmca] 2019*). Crizanlizumab-tmca was granted priority review, orphan drug and breakthrough therapy designations, and was approved on November 15, 2019 (*FDA Drug Approvals and Databases Web Site [crizanlizumab-tmca])*. Crizanlizumab-tmca must fulfill post-marketing requirements and commitments, monitoring for continued safety and efficacy.
  - Voxelotor, an HbS polymerization inhibitor, was FDA approved on November 25, 2019 under accelerated approval. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Voxelotor was granted priority review, fast track, orphan drug, rare pediatric disease, and breakthrough therapy designations (*FDA Drug Approvals and Databases Web Site [voxelotor]*). Voxelotor must fulfill post-marketing requirements and commitments, monitoring for continued safety and efficacy.
- The SCD agents included in this review are listed in Table 1 by brand name. Hydroxyurea products and L-glutamine used in the treatment of SCD are excluded from this review, but are included in separate reviews.

- Medispan classes: Crizanlizumab-tmca: Agents for sickle cell anemia, selectin blocker; Voxelotor: Agents for sickle cell anemia, HbS polymerization inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adakveo (crizanlizumab-tmca)	-
Oxbryta (voxelotor)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Adakveo (crizanlizumab-tmca)	Oxbryta (voxelotor)
To reduce the frequency of VOCs in adults and pediatric patients ≥ 16 years of age with SCD	✔	
Treatment of SCD in adults and in pediatric patients 12 years of age and older*		✔

*This indication is approved under accelerated approval based on increase in hemoglobin; continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

(*Prescribing information: Adakveo 2019, Oxbryta 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Crizanlizumab-tmca
  - The FDA approval of crizanlizumab-tmca was based on a Phase 2, multi-center (MC), double blind (DB), placebo controlled (PC), parallel group (PG), randomized controlled trial (RCT) (SUSTAIN trial) of 198 SCD patients that were randomized 1:1:1 to receive crizanlizumab-tmca 5 mg/kg, crizanlizumab-tmca 2.5 mg/kg, or placebo intravenously (IV) on weeks 0 and 2 and every 4 weeks thereafter for a total of 52 weeks (*Ataga et al 2017*). Hydroxyurea therapy was allowed if the patient was receiving it for ≥ 6 months and on a stable dose for ≥ 3 months prior to enrollment.
    - The primary endpoint was the annual rate of VOCs during the study period, defined as acute episodes of pain with no medically determined cause other than a VOC that resulted in a medical facility visit and treatment with oral or parenteral narcotic agents or with a parenteral NSAID. At the end of treatment, the median VOC rate per year in the intent-to-treat (ITT) population was 1.63 in the crizanlizumab-tmca 5 mg/kg group (FDA-approved dose), as compared with 2.98 in the placebo group (indicating a 45.3% lower rate with crizanlizumab-tmca than with placebo; p = 0.01). The median crisis rate in the 2.5 mg/kg crizanlizumab-tmca group was not significantly different from placebo.
    - A total of 24 of 67 patients (36%) in the crizanlizumab-tmca 5 mg/kg group and 11 of 65 patients (17%) in the placebo group had 0 VOCs during the treatment period.
    - The median time to the first VOC was significantly longer among patients receiving crizanlizumab-tmca 5 mg/kg than among those receiving placebo (4.07 vs 1.38 months, respectively; p = 0.001), as was the median time to the second VOC (10.32 vs 5.09 months, respectively; p = 0.02).
    - Assessment of quality of life (QOL) by the Brief Pain Inventory (BPI) questionnaire did not demonstrate significant changes from baseline during the trial for changes in pain severity or pain-interference.
    - Serious adverse events (SAEs) were reported in 55 patients, including 17 patients in both the crizanlizumab-tmca 5 mg/kg and placebo groups, respectively, and in 21 patients in the crizanlizumab-tmca 2.5 mg/kg treatment group. The SAEs that occurred in at least 2 patients in either crizanlizumab-tmca treatment arm and at a higher frequency than in the placebo arm were pyrexia (3% in the crizanlizumab-tmca 5 mg/kg group vs 0% in the crizanlizumab-tmca 2.5 mg/kg group vs 2% in the placebo group) and influenza (0% in the crizanlizumab-tmca 5 mg/kg group vs 5% in the crizanlizumab-tmca 2.5 mg/kg group vs 0% in the placebo group).

- Voxelotor
  - The approval of voxelotor was based on a Phase 3, MC, DB, PG, PC, RCT (HOPE trial) of 274 patients that were randomized 1:1:1 to receive either voxelotor 1500 mg, voxelotor 900 mg, or placebo orally once daily (*FDA Multidiscipline Review [OXBRYTA] 2018, Vichinsky et al 2019*). Enrolled patients had from 1 to 10 VOCs within the 12 months prior to enrollment and a baseline hemoglobin level ≥ 5.5 to ≤ 10.5 g/dL. Sixty-five percent of patients were on stable doses of hydroxyurea for at least 90 days prior to enrollment, and were allowed to continue therapy during the trial.
    - Overall, 83.9% (230 out of 274) of patients completed the study through week 24 (*FDA Multidiscipline Review [OXBRYTA] 2018*). The primary efficacy endpoint was a hemoglobin increase of > 1 g/dL from baseline to week 24. A change in hemoglobin by 1.0 g/dL is similar in magnitude to the effect of 1 unit of RBC transfusion; it is probable that an increase in hemoglobin would likely predict a decrease in stroke risk as measured by transcranial Doppler (TCD). However, verification and description of this clinical benefit is currently under investigation in confirmatory trials. The response rate for voxelotor 1500 mg (the FDA-approved dose) was 51.1% (46 out of 90), compared to 6.5% (6 out of 92) in the placebo group ($p < 0.001$).
      - The percentages of patients who underwent RBC transfusions during the trial period were similar in the 3 trial groups (33% in the voxelotor 1500 mg group, 32% in the voxelotor 900 mg group and 25% in the placebo group). Most transfusions were performed because of acute VOCs.
      - The percentages of participants who had at least 1 VOC were 67% in the voxelotor 1500 mg group, 66% in the voxelotor 900 mg group and 69% in the placebo group.
    - Secondary endpoints included the change in hemoglobin, percent change in indirect bilirubin, and percent reticulocyte count from baseline to week 24. In the voxelotor 1500 mg group, the mean changes from baseline to week 24 for hemoglobin, indirect bilirubin, and percent reticulocyte were 1.1 g/dL, -29.1%, and -19.9%, respectively. In the placebo group, the mean changes from baseline to week 24 for hemoglobin, indirect bilirubin, and percent reticulocyte were -0.1 g/dL, -3.2%, and 4.5%, respectively.
    - The most common adverse effects (AEs), with an incidence ≥ 20% were headache and diarrhea; the majority of AEs were grade ≤ 2.
    - SAEs, grade > 3 AEs, and number of patients who discontinued treatment did not differ substantially among the 3 groups. Most AEs were judged by the investigators to be unrelated to the trial drug or placebo.
    - No substantial differences in the percentages of patients who had SCD-related AEs among the treatment groups were observed (76% in the voxelotor 1500 mg treatment group and 73% in the placebo group, respectively).
    - Four deaths occurred during the trial (1 patient in the voxelotor 1500 mg group, 1 patient in the voxelotor 900 mg group, and 2 in the placebo group). None of the deaths were determined to be treatment-related.

CLINICAL GUIDELINES

- Currently in the U.S., there are no comprehensive, systematically reviewed, evidence-based guidelines for the management of SCD; however, NIH-sponsored, evidence-based expert consensus guidelines were published in 2014 *(NIH 2014)*. These guidelines provide recommendations for enhancing preventive care, managing the most common acute and chronic complications of SCD, and initiation and monitoring of the 2 available disease-modifying therapies for SCD, ie, hydroxyurea and blood transfusions. Additionally, HSCT provides hope for a cure for SCD; however, at present, the procedure is infrequently performed and very expensive. Additional research regarding patient and donor selection and the specific transplantation procedure is required before this potentially curative therapy will become more widely available.
  - Hydroxyurea and chronic blood transfusions are the 2 proven disease-modifying therapies for SCD. Both therapies are used in primary and secondary stroke prevention. Although neither has been shown to prevent all SCD-related organ damage, these treatment modalities can improve the QOL for individuals with SCD.
    - Treatment with hydroxyurea is underutilized for many people with SCA who could benefit from it. Blood transfusion therapy has at times been underutilized, overutilized, or prescribed inappropriately for both acute and chronic complications.
    - Recommendations for the use of hydroxyurea are as follows:
      - Adults with SCA who have ≥ 3 moderate to severe SCCs in a 12-month period should receive hydroxyurea (Strong recommendation, High-quality evidence).
      - Adults with SCA who have sickle cell-associated pain that interferes with daily activities and QOL should receive hydroxyurea (Strong recommendation, Moderate-quality evidence).

- Adults with a history of severe and/or recurrent ACS should receive hydroxyurea (Strong recommendation, Moderate-quality evidence).
- Adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities and QOL should receive hydroxyurea (Strong recommendation, Moderate-quality evidence).
- For infants ≥ 9 months of age, children, and adolescents, treatment with hydroxyurea should be offered regardless of clinical severity to reduce SCD-related complications (Strong recommendation, High-quality evidence for age 9 to 42 months; Moderate recommendation, Moderate-quality evidence for children > 42 months and adolescents).

▪ Recommendations for blood transfusions are as follows:
- Patients with SCD should not be routinely transfused for chronic anemia or uncomplicated pain crises without an appropriate clinical indication.
- There are many potential indications for transfusion in patients with SCD. The most common indications are prophylactic perioperative transfusion; transfusion in the setting of acute occurrences such as stroke, multisystem organ failure, and ACS; and transfusion in the setting of chronic occurrences such as primary and secondary prevention of stroke in children.
  - In children and adults who have had a stroke, a program of monthly simple or exchange transfusions should be initiated. (*Moderate strength, Low-Quality Evidence*)
  - In children and adults who have had a stroke, if it is not possible to implement a transfusion program, hydroxyurea therapy should be initiated. (*Moderate Strength, Low-Quality Evidence*)

- The guidelines have not been updated to include the use of L-glutamine for SCD or the newly FDA-approved crizanlizumab-tmca and voxelotor. Both crizanlizumab-tmca and voxelotor may be used concomitantly with hydroxyurea.

SAFETY SUMMARY

- Voxelotor is contraindicated in patients with a prior drug sensitivity to voxelotor or excipients. Clinical manifestations may include generalized rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia.
- Crizanlizumab-tmca has warnings and precautions for infusion-related reactions (eg, fever, chills, nausea, vomiting, urticaria, shortness of breath) and laboratory test interference (eg, platelet clumping, in particular when blood samples were collected in tubes containing ethylenediaminetetraacetic acid [EDTA]).
- Voxelotor has warnings and precautions for hypersensitivity reaction, which have occurred in < 1% of patients, and laboratory test interference with measurement of hemoglobin subtypes (ie, adult hemoglobin [HbA], sickle hemoglobin [HbS], and fetal hemoglobin [HbF]) by high-performance liquid chromatography.
- The most common AEs occurring in ≥ 10% of patients treated with crizanlizumab-tmca with a difference of > 3% compared to placebo are nausea (18%), arthralgia (18%), back pain (15%), and pyrexia (11%).
  - Clinically relevant AEs (all grades) reported in < 10% of patients included oropharyngeal pain, abdominal pain (abdominal pain, upper abdominal pain, lower abdominal pain, abdominal discomfort, and abdominal tenderness), diarrhea, vomiting, pruritis (pruritis and vulvovaginal pruritis), musculoskeletal chest pain, myalgia, infusion-site reaction (infusion-site extravasation, infusion-site pain, and infusion-site swelling), and infusion-related reaction.
- The safety profile observed in pediatric patients 12 to < 17 years of age treated with voxelotor was similar to that seen in adult patients. The most common AEs occurring in ≥ 10% of patients treated with voxelotor with a difference of > 3% compared to placebo are headache (26%), diarrhea (20%), abdominal pain (19%), nausea (17%), fatigue (14%), rash (4%), and pyrexia (12%). Clinically relevant AEs occurring in < 10% of patients included drug hypersensitivity.
- Voxelotor also carries warnings for drug-drug interactions:
  - Co-administration of strong cytochrome P450 (CYP) 3A4 inhibitors or fluconazole may increase voxelotor plasma concentrations and may lead to increased toxicity.
  - Co-administration of strong or moderate CYP3A4 inducers may decrease voxelotor plasma concentrations and may lead to reduced efficacy.
  - Voxelotor increased the systemic exposure of midazolam (a sensitive CYP3A4 substrate).
- Severe hepatic impairment increases voxelotor exposure, and the dose should be reduced. No dosage adjustment is required for patients with mild or moderate hepatic impairment.
- There are no available data on crizanlizumab-tmca or voxelotor use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnant women should be

advised of the potential risk to a fetus, and crizanlizumab-tmca or voxelotor should only be used during pregnancy if the benefit of the drug outweighs the potential risk.

- There are no data on the presence of crizanlizumab-tmca or voxelotor in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for SAEs in the breastfed child, patients should be advised that breastfeeding is not recommended during treatment with either agent, and for at least 2 weeks after the last voxelotor dose.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adakveo (crizanlizumab-tmca)	Injection	IV	Loading doses: weeks 0 and 2 Maintenance doses: every 4 weeks thereafter	May be administered with hydroxyurea
Oxbryta (voxelotor)	Tablets	Oral	Once daily	May be administered with hydroxyurea Tablets should be swallowed whole, and should not be cut, crushed, or chewed Reduce dose for hepatic impairment; dose adjust for drug-drug interactions

See the current prescribing information for full details

CONCLUSION

- SCD is a serious and life-threatening chronic disorder that affects approximately 100,000 individuals in the U.S.
- SCD patients frequently experience VOCs and typically have reduced hemoglobin levels, both of which contribute to frequent hospitalizations, and significant morbidity and early mortality.
- HSCT and gene therapy are the only curative options for SCD; however, only a small percentage of patients are eligible for these treatments. Current treatment options include symptom improvement and support to decrease the number of VOCs and increase hemoglobin levels.
- Prior to the approval of crizanlizumab-tmca and voxelotor, hydroxyurea was commonly used as a potentially disease-modifying pharmacologic treatment for SCD. Per NIH consensus treatment guidelines, hydroxyurea is considered the standard of care for both adults with painful SCCs and other chronic complications, and for pediatric patients regardless of clinical severity, to reduce SCD-related complications. However, hydroxyurea may be associated with significant toxicities that include myelosuppression. L-glutamine also received FDA approval for the treatment of SCD and has shown some effectiveness in reducing VOCs; however the data remain limited. No data are available with regard to the impact of L-glutamine on mortality or QOL. Use of L-glutamine is not addressed in the NIH consensus treatment guidelines, nor are crizanlizumab-tmca or voxelotor.
- There is currently an unmet need for effective options to treat SCD. Crizanlizumab-tmca and voxelotor may provide benefit to SCD patients who are inadequately managed by other treatment options, and may be used in combination with hydroxyurea. Crizanlizumab-tmca demonstrated a lower annual rate of VOCs versus placebo. Voxelotor demonstrated a 1 g/dL increase in hemoglobin levels vs placebo but data have not shown a reduction in RBC transfusions or VOCs. Longer-term efficacy data for both agents are lacking regarding morbidity and mortality, although in clinical trials, primary endpoints were met. The overall safety profile of both agents appears manageable and acceptable for patients, although both agents are required to fulfill post-marketing requirements that continue monitoring safety and efficacy.

REFERENCES

- Adakveo [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2019.
- Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the prevention of pain crises in sickle cell disease. *N Engl J Med*. 2017;376(5):429-439.
- Centers for Disease Control and Prevention (CDC). Sickle Cell Disease (SCD). CDC Web site. https://www.cdc.gov/ncbddd/sicklecell/data.html. Accessed January 7, 2020.
- Department of Health and Human Services. National Institutes of Health (NIH). National Heart, Lung, and Blood Institute. Evidence-based management of sickle cell disease. Expert panel report, 2014. https://www.nhlbi.nih.gov/sites/default/files/media/docs/sickle-cell-disease-report%20020816_0.pdf. Accessed January 3, 2020.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 3, 2020.
- Field JJ, Vichinsky EP. Overview of the management and prognosis of sickle cell disease. UpToDate Web site. Updated September 7, 2018. www.uptodate.com. Accessed January 7, 2020.
- Food and Drug Administration. Drug Approvals and Databases. Crizanlizumab-tmca 2019. FDA Web site. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-crizanlizumab-tmca-sickle-cell-disease. Accessed January 8, 2020.
- Food and Drug Administration. Drug Approvals and Databases. Voxelotor 2019. FDA Web site. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-voxelotor-sickle-cell-disease. Accessed January 8, 2020.
- Food and Drug Administration. Multidiscipline Review: Adakveo. 2018. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761128Orig1s000MultidisciplineR.pdf. Accessed January 3, 2020.
- Food and Drug Administration. Multidiscipline Review: Oxbryta. 2018. FDA Web site. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/213137Orig1s000Multidiscipline.pdf. Accessed January 3, 2020.
- Food and Drug Administration Press Release: FDA approves first targeted therapy to treat patients with painful complication of sickle cell disease (crizanlizumab-tmca). FDA Web site. https://www.fda.gov/news-events/press-announcements/fda-approves-first-targeted-therapy-treat-patients-painful-complication-sickle-cell-disease. Accessed January 9, 2020.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 3, 2020.
- Oxbryta [package insert], San Francisco, CA: Global Blood therapeutics, Inc.; November 2019.
- Vichinsky E, Hoppe CC, Ataga KI, et al. A phase 3 randomized trial of voxelotor in sickle cell disease. *N Engl J Med*. 2019 Aug 8;381(6):509-519.
- Vichinsky EP, Mahoney DH. Diagnosis of sickle cell disorders. UpToDate Web site. Updated April 26, 2018. www.uptodate.com. Accessed January 7, 2020.

Publication Date: January 22, 2020