

Brand Name: Oxbryta

Generic Name: voxelotor

Manufacturer⁴: Global Blood Therapeutics

Drug Class^{2,3,4}: Hemoglobin S polymerization Inhibitor

Uses^{2,3,4}:

Labeled Uses: Sickle Cell Disease (SCD)

Unlabeled Uses: N/A

Mechanism of Action: Binds to hemoglobin S and exhibits preferential partitioning to red blood cells. Increases affinity of hemoglobin for oxygen and exhibits a dose dependent inhibition of hemoglobin S.

Pharmacokinetics^{1,2,3,4}

Absorption:

T _{max}	2 hours
V _d	338 L in central and peripheral compartment 72.2 L in plasma
t _{1/2}	35.5 hours
Clearance	6.7 L/h
Protein binding	99.8%
Bioavailability	NA

Metabolism:

Metabolized through phase I oxidation and reduction, phase II glucuronidation, and combination of phase I and II metabolism. Oxidation of voxelotor is mediated by CYP3A4, with minor contributions from CYP2C19, CYP2B6, and CYP2C9.

Elimination.

62.6% dose and its metabolites excreted into feces (33.3%) unchanged and 35.5% in urine (0.08%) unchanged

Efficacy:^{5,6}

Howard J, Hemmaway CJ, Telfer P, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. *Blood*. 2019;133(17):1865-1875. doi:10.1182/blood-2018-08-868893

Study Design: randomized, doubled blind, placebo-controlled study of voxelotor in healthy volunteers and patients with SCD

Description of Study: *Methods:* The objective of the study was to evaluate safety, tolerability, pharmacokinetic, and pharmacodynamic properties of voxelotor in SCD. Patients were included in the study if they had SCD, were between ages 18-60 years old, and had a weight > 50kg at the time of screening. Women and men who were of childbearing age were required to use contraception throughout the study. A total of 52 patients were recruited for the study. The patients were initially assigned to two cohorts: 28 days and 90 days. Patients in the 28 days cohort were further broken up to receive 700 mg/d, 500 mg/d, or 1,000 mg/d voxelotor or placebo. Meanwhile patients in the 90-day group received 700 mg/d, 900 mg/d voxelotor or placebo. **Efficacy** was assessed by standard clinical hematology measures. For patients enrolled in the 28 day cohorts, hematology laboratory measure were collected at screening and baseline and on days 4,8,15,22 and 28. For patients enrolled in the 90 day cohort, hematology laboratory measures were collected at screening and baseline, on days 4,15, 22,28, 44, 60, 70, and 90. Safety was assessed in all patients who received at least 1 dose of the study drug. The **safety assessments** included symptoms inquiry, physical examinations, vital signs, standard clinical laboratory tests, complete hematology panel, urinalyses, pregnancy tests, 12 lead electrocardiogram, and adverse events reporting from the time of study drug administration to 30 days after the last dose of study drug.

Results: For the efficacy outcome, all groups who received voxelotor for 90 days showed a significant increase in hemoglobin ($p < 0.05$) with the median increase being 1g/dl, significant decreases in unconjugated bilirubin, percentage of reticulocytes and sickled red cells ($p < 0.05$). The other results were not significant. In terms of safety, treatment emergent adverse effects occurred in more than 10% of the patients. However, the side effects were a grade 1 or grade 2 (mild to moderate headaches, back pain, cough, rash, and diarrhea). Of note, there were 12 serious adverse effects that did occur in patients who received voxelotor such as a sickle cell anemia with crisis but were reported as not being related to the treatment. One patient did discontinue the study treatment due to a grade 2 rash.

Limitations: The efficacy outcomes for changes in hemolysis to day 28 were not reported with a p value or a confidence interval to show significance. Also, there was an unequal amount of people in the study drug and placebo groups, which could skew the results by not giving an accurate representation of the placebo groups. Authors were consultants with Global Blood Therapeutics, the manufacture for voxelotor, which could lead to bias. A sample size of 52 patients may be too small to evaluate the efficacy and safety of the medication.

Conclusion: The study showed that voxelotor is effective at raising hemoglobin in patients with SCD and is relatively safe. However, more studies need to be conducted to confirm the results of this study with a larger sample size.

Vichinsky E, Hoppe CC, Ataga KI, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *N Engl J Med.* 2019;381(6):509-519. doi:10.1056/NEJMoa1903212

Study Design: Multicenter, phase 3, double blind, randomized, placebo-controlled trial

Description of Study: Methods: The study's objective was to evaluate efficacy and safety of voxelotor against a placebo in adolescents and adults with SCD. Patients were included if they were between 12 and 65 years old, had confirmed SCD, hemoglobin level between 5.5 and 10.5 g per deciliter, and had a 1 to 10 vaso-occlusive crises (VOC) in the past 12 months (defined as acute painful crisis or acute chest syndrome for which there was no other explanation). Patients were excluded if they had more than 10 VOCs within the past 12 months that required hospitalization, receive red blood cell transfusions regularly, hospitalized for sickle cell crisis or other vaso-occlusive event within 14 days of signing the informed consent form, hepatic dysfunction (ALT > 4 x ULN), and severe renal dysfunction (eGFR < 30 ml/min). Total of 274 participants were randomly assigned in a 1:1:1 ratio to receive a once daily oral dose of 1,500 mg of voxelotor, 900 mg of voxelotor, or placebo. Participants had sickle cell anemia (homozygous hemoglobin S, sickle hemoglobin C disease, hemoglobin S β -thalassemia, or other genotypic variants of sickle cell disease) and roughly two thirds were receiving hydroxyurea at baseline. **The primary endpoint** was the percentage of participants who had a hemoglobin response, which was defined as an increase of more than 1.0 g per deciliter from baseline at week 24 in the intention to treat analysis. **The secondary endpoints** were a change in hemoglobin from baseline to week 24, indirect bilirubin level, absolute reticulocyte count, percentage of reticulocytes, lactate dehydrogenase level, and incidence rate of VOC along with other adverse events.

Results: There was a significantly higher percentage of participants who had a hemoglobin response at week 24. Hemoglobin levels increased 51% in the 1500-mg voxelotor group and 7% in placebo group. Anemia worsened between baseline and week 24 in fewer participants in each voxelotor dose group than in those receiving placebo. At week 24, the 1500-mg voxelotor group had significantly greater reductions from baseline in the indirect bilirubin level and percentage of reticulocytes than the placebo group. Additionally, group, 26% of the participants in the 1500 mg group had at least a grade 3 adverse event, 23% in the 900 mg voxelotor group, and 26% in the placebo group. It is important to note that four participants did have a fatal adverse event (one participant in the 1,500 voxelotor group had pulmonary sepsis, sickle cell anemia with crisis, and acute sickle cell hepatic crisis; one participant in the 900 mg voxelotor group had sickle cell anemia with crisis; one participant in the placebo group had sickle cell anemia with crisis; and one participant in the placebo group had cardiac arrest). The authors noted that the adverse events were not related to the trial drug or placebo.

Limitations: There is a potential for conflicts of interest given that seven of the authors were employees or owned shares at Global Blood Therapeutics. The results of this study should be interpreted with caution. The authors did not report the power of study.

Conclusion: The study showed that voxelotor is effective at increasing the hemoglobin level and reducing the incidence of worsening anemia. Future studies should study the effects of voxelotor on pregnancies as there is not enough information on using voxelotor during pregnancy.

Hutchaleelaha A, Patel M, Washington C, et al. Pharmacokinetics and pharmacodynamics of voxelotor (GBT440) in healthy adults and patients with sickle cell disease. *Br J Clin Pharmacol.* 2019;85(6):1290-1302. doi:10.1111/bcp.13896

Study Design⁷: Two center, randomized, double blind, placebo-controlled study

Description of Study: *Methods:* The study's objectives were to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy participants and patients who had SCD. Healthy participants were included if they were between ages 18 and 55 years old, > 50 and < 110 kg, at time of screening, negative illicit drug test, and women of childbearing age had to use effective methods of contraception from start of study to three months after the last dose. Healthy participants were excluded if they had a clinically relevant surgical or family history, used prescription drugs within four weeks of first dose of study drug, and use over the counter medications excluding routine vitamin. SCD participants were included if they were between 18 and 60 years old, weight > 50 kg at time of screening with homozygous hemoglobin S, sickle hemoglobin C disease or, hemoglobin S β -thalassemia, negative illicit drug test, and women of childbearing age used effective contraception methods. SCD participants were excluded if smoke more than 10 cigarettes per day, hemoglobin < 6 or > 10.4, undergoing chronic transfusion therapy, had blood transfusions within 30 days of screening, or hospitalized within 30 days of screening. A total of 40 healthy volunteers were assigned to either get 100 mg, 400 mg, 1,000 mg, 2,000 mg, or 2,800 mg of voxelotor or placebo. The groups were split up with a 6:2 ratio. There were 8 sickle cell disease (SCD) patients who received 1,000 mg voxelotor or placebo in a 6:2 ratio. Twenty-four other healthy volunteers received multiple doses of voxelotor once daily for 15 days of strengths 300 mg, 600 mg, 900 mg, or placebo split up with a 6:2 ratio. The goal of this study was to see the safety and tolerability of voxelotor.

Results: Patients in the healthy volunteer group who received a single dose of voxelotor, 10% had diarrhea, 6.7 % had an upper respiratory tract infection, 6.7% had arthralgia. 6.7% had headache, and 6.7% had a rash. Compared to the placebo group, 10% had an upper respiratory tract infection, headache, and rash. In the group of patients who received 15 days of voxelotor or placebo, 11.1 % had abdominal pain, gastroenteritis, and dizziness, 16.7% of the patients had diarrhea, and 27.8 % had headaches. Overall, voxelotor was well tolerated with the patients with no serious adverse events occurring.

Limitations: Unblinding could have occurred due to placebo not being associated with side effects such as diarrhea or upper respiratory tract infections. No significance value was reported for the results.

Conclusion: In conclusion, the adverse events from voxelotor were mild with the most common event being headaches. However, due to the small sample size, varying dosing of voxelotor, and potential conflicts of interest with the authors being affiliated with Global Blood Therapeutics, the results should be taken with caution.

Contraindications^{1,2,3,4}:

Prior drug hypersensitivity to voxelotor or excipients

Precautions^{1,2,3,4}:

Hypersensitivity Reactions

- Serious hypersensitivity reactions have occurred in < 1% of the patients treated after administration of Oxbryta.
 - can occur with a rash, urticaria, shortness of breath, mild face swelling, and eosinophilia
- If hypersensitivity reaction occurs, discontinue Oxbryta and administer appropriate medical therapy. Do not reinstate Oxbryta if patients experience these symptoms

Laboratory Test Interference

- Oxbryta administration might interfere with hemoglobin subtypes (HbA, HbS, and HbF) by high performance liquid chromatography. Chromatography should not be performed when the patient is receiving Oxbryta therapy

Adverse Effects^{1,2,3,4}:

Occurring in >10% of patients

Abdominal pain (19%) | Diarrhea (20%) | Fatigue (14%) | Fever (12%) | Headache (26%)
| Nausea (17%) | Rash (14%)

Occurring in >1% to <10% of patients³

Hypersensitivity reaction (<10%)

Drug Interactions^{1,2,3}

CYP3A4 inhibitors may increase the serum concentration of CYP3A4 substrates while 3A4 inducers decrease the serum concentrations

Inhibitors:

Abametapir, Aprepitant, Clofazimine, Conivaptan, Dofetilide, Duvelisib, Erdafitnib, Flibanserin, Fluconazole, Fosaprepitant, Fosnetupitant, Fusidic Acid, Idelalisib, Larotrectinib, Lemborexan, Lomitapide, MiFEPRISone, Netupitant,

NiMODipine, Palbociclib, Pimozide, Simeprevir, Stiripentol, Tacrolimus, Triazolam, Ubrogapant

Inducers:

Dabrafenib, Deferasirox, Enzalutamide, Erdafitnib, Ivosidenib, Mitotane, Sarilumab, Siltuximab, Tocilizumab

Dosing/Administration ^{1,2,3,4}:

Adult dosing and Elderly: 1,500 mg PO once daily

Children and Adolescents 12-17 years old: 1,500 mg PO once daily

Hepatic Impairment (severe, Child Pugh C): Reduce dose to 1,000 mg PO once daily

Renal Impairment: No dose adjustment needed

Use in special circumstances ^{1,2,3,4}:

Pregnancy: No data available

Lactation: Breast-feeding not recommended during treatment with voxelotor and for at least 2 weeks after the last dose

Cost Comparison ⁸:

The Institute for Clinical and Economic Review compared medications used for SCD such as L-glutamine, crizanlizumab, voxelotor, and hydroxyurea. The net prices per year are: \$10,031 - \$30,092, \$35,355- \$176,775, \$100,000, and \$322 – \$2,251 respectively.

Conclusion:

Voxelotor is an effective therapy for patients with sickle cell disease and seems to be fairly well tolerated. More studies need to be conducted to evaluate its efficacy in the geriatric and pediatric populations. More studies also need to be done to see its effects during pregnancy. The cost of voxelotor will be a major barrier as Some other currently available treatment options are less costly. Voxeleotor should be considered when other options have failed or are not tolerated.

References:

1. Voxelotor. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo:Thomson Micromedex. Updated periodically. Accessed: October 20, 2020.
2. Voxelotor. Clinical Pharmacology [Internet Database]. Gold Standard, Inc., 2020.Available at: <http://www.clinicalpharmacology.com>Accessed: October 20, 2020
3. Voxelotor. Lexi-Drugs [database online]. Lexi-Comp, Inc; October 20, 2020.
4. Voxelotor [package insert]. South San Francisco, CA: Global Blood Therapeutics, Inc, October 20,2020.

5. Howard J, Hemmaway CJ, Telfer P, et al. A phase 1/2 ascending dose study and open-label extension study of voxelotor in patients with sickle cell disease. *Blood*. 2019;133(17):1865-1875. doi:10.1182/blood-2018-08-868893
6. Vichinsky E, Hoppe CC, Ataga KI, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. *N Engl J Med*. 2019;381(6):509-519. doi:10.1056/NEJMoa1903212
7. Hutchaleelaha A, Patel M, Washington C, et al. Pharmacokinetics and pharmacodynamics of voxelotor (GBT440) in healthy adults and patients with sickle cell disease. *Br J Clin Pharmacol*. 2019;85(6):1290-1302. doi:10.1111/bcp.13896
8. Institute for Clinical and Economic Review. Crizanlizumab, L-Glutamine, and Voxelotor for Sickle Cell Disease: Effectiveness and Value. Available: https://icer-review.org/wp-content/uploads/2019/08/ICER_SCD_MAP_112119.pdf. Accessed: November 5, 2020.

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