

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213137Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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<b>Application Type</b>	NDA
<b>Application Number</b>	213137
<b>PDUFA Goal Date</b>	November 25, 2109
<b>OSE RCM #</b>	2019-1368 and 1370
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<b>Review Completion Date</b>	November 20, 2019
<b>Subject</b>	Evaluation of Need for a REMS
<b>Established Name</b>	Voxelotor
<b>Trade Name</b>	Oxybryta
<b>Name of Applicant</b>	Global Blood Therapeutics, Inc.
<b>Therapeutic Class</b>	A hemoglobin S polymerization inhibitor
<b>Formulation(s)</b>	500 mg tablet
<b>Dosing Regimen</b>	1500 mg taken orally once daily

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## EXECUTIVE SUMMARY

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Oxybryta (voxelotor) is necessary to ensure the benefits outweigh its risks. Global Blood Therapeutics, Inc. (GBT) submitted New Drug Application (NDA) 213137 for voxelotor with the proposed indication for the treatment of sickle cell disease (SCD) in adult and pediatric patients 12 years of age and older. This indication will be approved under accelerated approval based on increase in hemoglobin (Hb) contingent upon verification of the clinical benefit in the confirmatory trial. The risks associated with voxelotor include hypersensitivity reactions and laboratory test interference. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRISK) has determined that a REMS is not needed to ensure the benefits of voxelotor outweigh its risks. SCD is an inherited, lifelong blood disease that can cause significant morbidity and early mortality. The pharmacotherapy treatment options for SCD are limited to only two FDA approved medications, hydroxyurea(HU) and L-glutamine. There remains a need for effective and safe pharmacotherapy to treat SCD.

The clinical trial for voxelotor demonstrated that voxelotor improved Hb significantly and reduced some clinical measures of hemolysis with a well tolerated safety profile. The risks associated with voxelotor include hypersensitivity reactions and interference with laboratory testing that use high performance liquid chromatography (HPLC) to measure of Hb subtypes (HbA, HbS, and HbF). If approved, these risks will be communicated in the warning and precaution section of the prescribing information. A REMS is not necessary to ensure the risks outweigh the benefits of voxelotor.

## 1 Introduction

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This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Oxybryta (voxelotor) is necessary to ensure the benefits outweigh its risks. Global Blood Therapeutics, Inc. (GBT) submitted New Drug Application (NDA) 213137 for voxelotor with the proposed indication for the treatment of sickle cell disease (SCD) in adult and pediatric patients 12 years of age and older. This indication will be approved under accelerated approval based on increase in hemoglobin (Hb) contingent upon verification of the clinical benefit in the confirmatory trial. The applicant did not submit a proposed REMS or risk management plan with this application, but did propose a Patient Package Insert (PPI).

## 2 Background

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### 2.1 PRODUCT INFORMATION

Voxelotor, a new molecular entity,<sup>a</sup> is a hemoglobin S polymerization inhibitor, proposed for the treatment of sickle cell disease in adult and pediatric patients 12 years of age and older. Voxelotor can be administered alone or in combination with HU. Voxelotor binds to HbS with a 1:1 stoichiometry and

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

exhibits preferential partitioning to red blood cells (RBCs). By increasing the affinity of Hb for oxygen, voxelotor shows dose-dependent inhibition of HbS polymerization.<sup>1</sup> Voxelotor is proposed as a 500 mg tablet taken orally with the usual dose of 1500 mg once daily for the patient's life time.<sup>b</sup> Voxelotor is not currently approved in any jurisdiction.

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for voxelotor NDA 213137 relevant to this review:

- 10/07/2015: Fast track designation granted
- 12/29/2015: Orphan drug designation granted
- 06/05/2017: Rare pediatric disease designation granted
- 01/03/2018: Breakthrough therapy designation granted
- 03/29/2019: Original NDA 213137, 1<sup>ST</sup> (nonclinical) of 2 reviewable units of rolling NDA submitted
- 06/26/2019: 2<sup>ND</sup> and final reviewable unit of rolling NDA for accelerated approval submitted.
- 10/07/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for voxelotor.

## 3 Therapeutic Context and Treatment Options

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### 3.1 DESCRIPTION OF THE MEDICAL CONDITION

SCD is caused by an inherited mutation in hemoglobin (Hb) that leads to the production of sickle Hb (HbS). Normal RBCs contain 96%-98% HbA and have a biconcave shape that facilitates blood circulation and oxygen distribution to tissues. In SCD, a mutation occurs in the gene responsible for beta globin production which causes increased hydrophobic and reduced solubility of HbS. Polymerization also occurs which distorts RBCs into a sickle shape. Sickled RBCs increase blood viscosity leading to hypoxia and disease manifestations. During periods of deoxygenation, Hb S polymerizes within erythrocytes resulting vaso-occlusive crisis (VOC) and chronic hemolytic anemia. Vaso-occlusion occurs as a result of the formation of multi-cellular aggregates that block blood flow in small blood vessels, causing tissue ischemia and reperfusion damage to downstream tissues that lead to acute pain/crises episodes. SCD is associated with decreased life expectancy. Acute chest syndrome (ACS) is a serious acute complication and a leading cause of mortality in patients with SCD. Other causes of death in patients with SCD include infections and cerebrovascular events.<sup>c</sup>

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<sup>b</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (D): *The expected or actual duration of treatment with the drug.*

<sup>c</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

More than 300,000 children are born with SCD worldwide every year.<sup>2</sup> It is estimated nearly 100,000 individuals in the US have SCD.<sup>d</sup> Homozygous Hb SS is the most common form of SCD, which accounts for 60%-75% of SCD in the US. About 25% of patients have co-inheritance of Hb S with another  $\beta$ -globin chain variant, such as sickle-Hb C disease and sickle  $\beta$ -thalassemia.

### 3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Evidence-based recommendations for the management of SCD were published in 2014 by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) and endorsed by a number of societies including the American Academy of Pediatrics and the American Society of Hematology.<sup>3</sup> Hemolysis and vaso-occlusive phenomena are the clinical hallmarks of SCD. Vaso-occlusion results in recurrent painful episodes (sickle cell crisis) and a variety of serious organ system complications. These crisis and complications can lead to life-long disability and even death. The management of SCD include prevention of complications, treatment of complications, and the potential cure by hematopoietic stem cell transplantation (HSCT); however, only a few patients are eligible for a HSCT option.

- Prevention of complications – Primary prevention of acute complications includes routine health management with a health care provider with expertise in SCD. The use of penicillin prophylaxis started in the newborn period, immunizations, and blood transfusions for those at risk for stroke are initial steps to prevent complications. The only FDA approved therapies to prevent pain episodes in SCD are hydroxyurea (trade name Droxia) and pharmaceutical-grade L-glutamine (trade name Endari).<sup>3</sup>
  - Droxia (Hydroxyurea [HU]) was approved by the FDA in 1998 to reduce the frequency of painful crisis and to reduce the need for blood transfusions in patients with recurrent moderate to severe painful crisis. The use of HU is a mainstay in the overall management of patients with SCD since it reduces the incidence of acute painful episodes and hospitalization rates, and prolongs survival.

Droxia is an antimetabolite cytotoxic drug and carries a boxed warning for myelosuppression and malignancies.<sup>4</sup> A Medication Guide is provided for patients who use Droxia to discuss the risks of low blood counts and cancer.
  - Pharmaceutical grade L-glutamine oral powder (trade name Endari) is an oral medication approved by the FDA in 2017 to reduce acute complications of SCD in adults and pediatric patients 5 years of age and older. L-glutamine, an amino acid, was previously approved as NutreStore for the treatment of short bowel syndrome in patients receiving specialized nutritional support when used in conjunction with a recombinant

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<sup>d</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

human growth hormone. The mechanism is not fully understood, but is thought to involve an antioxidant effect. Oxidative stress phenomena are involved in the pathophysiology of SCD. While HU is first line therapy, L-glutamine provides a 2nd line therapy for patients who have a suboptimal response to HU or who do not tolerate HU.

The label for Endari does not include any Warnings and Precautions section, only an adverse reactions section: the most common adverse reactions are constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain. There is no Medication Guide or Patient Information for Endari.

- Treatment of complications of SCD – include pain management for vaso-occlusive events, hydration, blood transfusion, Incentive spirometry (to reduce the risk of acute chest syndrome), thromboembolism prophylaxis, and antibiotics for infection.

## 4 Benefit Assessment

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Efficacy of voxelotor was demonstrated in the HOPE study (NCT 03036813), a randomized, double-blind, placebo-controlled, multicenter trial. In this study, 274 patients were randomized to daily oral administration of voxelotor 1500 mg (N=90), 900 mg (N=92), or placebo (N=92).<sup>1</sup> Inclusion criteria was patient had 1 to 10 VOC events within 12 months and baseline Hb $\geq$ 5.5 to  $\leq$ 10.5 g/dL. Eligible patients on stable doses of HU for at least 90 days were allowed to continue HU therapy throughout the trial. The trial excluded patients who received RBC transfusions within 60 days and erythropoietin within 28 days, had renal insufficiency or uncontrolled liver disease or were pregnant or lactating.

Ninety percent of enrolled patients were HBSS or HbS $\beta$ 0thal genotype and 65% patients were receiving HU therapy. The mean age was 28 years (12-64 years); 17% patients were adolescents (12 to <18 years). Median baseline Hb was 8.5 g/dl (5.9-10.8 g/dL). Forty-two percent patients had 1 VOC event and 58% had 2-10 events within 12 months prior to enrollment.

Efficacy was based on Hb response rate defined as a Hb increase of >1 g/dL from baseline to week 24. The response rate for voxelotor 1500 mg was 51% compared to 6.5% in the placebo arm (p<0.001).<sup>e</sup> Change in Hb, percent change in indirect bilirubin, and percent reticulocyte count from baseline to week 24 were included in additional efficacy evaluation as shown in Table 1.

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<sup>e</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

**Table 1:** Adjusted mean change from baseline to week 24 in Hb and clinical measures of hemolysis

	Voxelotor 1500 mg qd, N=90	Placebo, N=92	P value
Hb	1.14 g/dL	-0.08 g/dL	<0.001
Indirect Bilirubin	-29%	-3.2%	<0.001
Percent Reticulocyte count	-19.9%	4.5%	<0.01

The statistical reviewer concluded at the internal Mid-cycle meeting, “In this study, voxelotor was shown to significantly improve Hb and reduce some clinical measures of hemolysis in adult and adolescent subjects with SCD.”<sup>4</sup>

## 5 Risk Assessment & Safe-Use Conditions

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In the HOPE study, four patients had fatal adverse events. One patient in the 1500 mg arm had pulmonary sepsis, sickle cell anemia with crisis, and acute sickle hepatic crisis; one in the 900 mg arm had sickle cell anemia with crisis; one in the placebo arm had sickle cell anemia with crisis; and one in the placebo arm had cardiac arrest.<sup>5</sup> The investigators determined that all deaths were not related to the trial drug or placebo.

The safety of voxelotor was evaluated in 88 patients who received voxelotor 1,500 mg and 91 patients who received placebo orally once daily. The median age of patients who received voxelotor was 24 years (range: 12-59). Among these patients, 65% were female and 65% received HU as baseline. The ethnic groups included 66% African American and 23% Arab/Middle Eastern.

At the time of this writing, labeling negotiations were still ongoing. The following section is a summary of safety information to date for voxelotor.

### 5.1 HYPERSENSITIVITY REACTIONS

Serious hypersensitivity reactions were observed in the clinical trial. The signs and symptoms of hypersensitivity included generalized rash, urticaria, mild shortness of breath, mild facial swelling, and eosinophilia. The prescribing information in Warnings & Precautions will advise healthcare providers to discontinue the drug and administer appropriate medical therapy. Healthcare providers will be also advised not to re-initiate voxelotor in patients who had serious hypersensitivity reactions.

### 5.2 Laboratory Test Interference

High Performance Liquid Chromatography (HPLC) measures of Hb subtypes (HbA, HbS, and HbF) may be interfered with administration of voxelotor. HPLC should be performed when the patient is not receiving voxelotor if precise quantitation of Hb species is required. Healthcare providers will be advised about this laboratory test interference in Warnings & Precautions, as well as in the Drug Interactions section of the prescribing information.

## **6 Expected Postmarket Use**

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If approved, voxelotor will be prescribed by various healthcare providers, such as hematologists, internists, general pediatricians, and family practitioners in both inpatient and outpatient settings.

## **7 Risk Management Activities Proposed by the Applicant**

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The Applicant did not propose any risk management activities for voxelotor beyond routine pharmacovigilance and labeling, which includes a Patient Information that discusses the risk of hypersensitivity reactions.

## **8 Discussion of Need for a REMS**

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The Clinical Reviewer recommends approval of voxelotor on the basis of the efficacy and safety information currently available.<sup>6</sup>

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for voxelotor, this reviewer considered the patient population likely to receive the drug, the seriousness of the disease, the expected benefit of the drug, the expected duration of treatment, and the seriousness of known or potential adverse events.

It is estimated nearly 100,000 individuals in the United States have SCD. The quality of life of these patients remains poor, often exhibited by recurrent, unpredictable, and painful sickle cell crises, with life expectancy reduced by 20-30 years. The FDA-approved pharmacotherapy treatment options for SCD are limited to HU and L-glutamine, as discussed above.

Voxelotor is a Hb S polymerization inhibitor proposed for the indication for the treatment of SCD in adult and pediatric patients 12 years of age and older. Voxelotor can be administered alone or in combination with HU, is taken orally once daily, and is possibly a lifelong therapy. In the clinical trial, voxelotor was shown to significantly improve Hb and reduce some clinical measures of hemolysis with a well tolerated safety profile. The possible risks are hypersensitivity reaction and interference with measurement of Hb subtypes that will be communicated in the prescribing information in Warnings and Precautions, including a Patient Information.

The prescribing information of voxelotor will communicate the risks of hypersensitivity reactions and laboratory test interference. A REMS is not necessary to ensure the risks outweigh the benefits of voxelotor.

## **9 Conclusion & Recommendations**

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Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for voxelotor to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety

information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

## 10 Appendices

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### 10.1 REFERENCES

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<sup>1</sup> Voxelotor draft prescribing information for voxelotor, 11/06/2019

<sup>2</sup> Sins JWR, Mager DJ, et al. Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review. *Blood Advances* 2017 1:1598-1616

<sup>3</sup> Field JJ, Vichinsky EP, Overview of the management and prognosis of sickle cell disease, [www.uptodate.com](http://www.uptodate.com) accessed 09/25/2019

<sup>4</sup> Luo, L. statistical reviewer. Slides presentation of voxelotor NDA 213137 Internal Mid-cycle meeting, 09/17/2019

<sup>5</sup> Vichinsky E, Hoppe CC, et al. A phase 3 randomized trial of voxelotor in sickle cell disease, [www.nejm.org/doi/10.1056/NJEMoa1903212](http://www.nejm.org/doi/10.1056/NJEMoa1903212), Aug.8, 2019

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