CLINICAL UPDATE

Brand Name	Oxbryta®
Generic Name	voxelotor
Drug Manufacturer	Global blood therapeutics

Clinical Update

TYPE OF CLINICAL UPDATE

Indication and Usage; Dosage and Administration.

FDA APPROVAL DATE

December 17, 2021

LAUNCH DATE

December 21, 2021

REVIEW DESIGNATION

Priority; Orphan

TYPE OF REVIEW

Type 3 - New Dosage Form; New Drug Application (NDA) 216157

DISPENSING RESTRICTIONS

Limited distribution

Overview

INDICATION(S) FOR USE

Oxbryta® is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 4 years of age and older. This indication is approved under accelerated approval based on increase in hemoglobin (Hb). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

MECHANISMS OF ACTION

Voxelotor inhibits hemoglobin S (HbS) polymerization, the central abnormality in sickle cell disease, by binding to HbS, which allosterically modifies hemoglobin and increases the affinity of Hb for oxygen. Consequently, voxelotor improves red blood cell (RBC) deformity, inhibits RBC sickling, and reduces whole blood viscosity.

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 500 mg; Tablets for oral suspension: 300 mg.

DOSE & ADMINISTRATION

Oxbryta® can be taken with or without food.

Recommended Dosage for Adults and Pediatric Patients 12 Years and Older:

The recommended dosage of Oxbryta® is 1,500 mg orally once daily.

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Recommended Dosage for Pediatric Patients 4 Years to Less Than 12 Years:

For pediatric patients 4 years and older, select the appropriate product (Oxbryta® tablets or Oxbryta® tablets for oral suspension) based on patient's ability to swallow tablets and patient weight.

Table 1: Recommended OXBRYTA Dosage in Pediatric Patients 4 Years to Less Than 12 Years

Body Weight	Recommended Dose (once daily)
40 kg or greater	1,500 mg
20 kg to less than 40 kg	900 mg
10 kg to less than 20 kg	600 mg

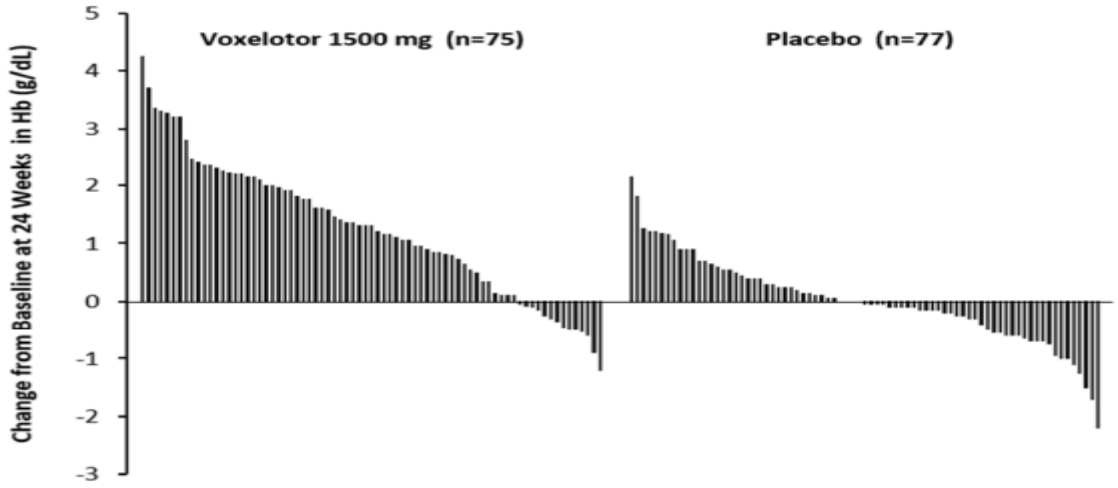
EFFICACY

Adults and Pediatric Patients 12 Years and Older-

The efficacy and safety of Oxbryta® in SCD was evaluated in HOPE, a Phase 3 randomized, double-blind, placebo-controlled, multicenter trial [NCT 03036813]. In this study, 274 patients were randomized to daily oral administration of Oxbryta® 1,500 mg (N=90), Oxbryta® 900 mg (N=92), or placebo (N=92). Patients were included if they had from 1 to 10 vasoocclusive crisis (VOC) events within 12 months prior to enrollment and baseline hemoglobin (Hb) ≥5.5 to ≤10.5 g/dL. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. Randomization was stratified by patients already receiving hydroxyurea (yes, no), geographic region (North America, Europe, Other), and age (12 to < 17 years, 18 to 65 years). The trial excluded patients who received red blood cell (RBC) transfusions within 60 days and erythropoietin within 28 days of enrollment, had renal insufficiency, uncontrolled liver disease, were pregnant, or lactating.

Efficacy was based on Hb response rate defined as a Hb increase of >1 g/dL from baseline to Week 24 in patients treated with Oxbryta® 1,500 mg versus placebo. The response rate for Oxbryta® 1,500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group ($p < 0.001$). No outlier subgroups were observed. The distribution of Hb change from baseline for individual patients completing 24 weeks of treatment with Oxbryta® 1,500 mg or placebo.

Figure 1: Subject-level Change from Baseline in Hemoglobin at Week 24 in Patients Who Completed 24 Weeks of Treatment*



Additional efficacy evaluation included change in Hb and percent change in indirect bilirubin and percent reticulocyte count from baseline to Week 24.

Table 2: Adjusted Mean (SE) Change from Baseline to Week 24 in Hemoglobin and Clinical Measures of Hemolysis

	OXBRYTA 1,500 mg QD (N=90)	Placebo (N=92)	P Value
Hemoglobin	1.1 g/dL (0.1)	-0.1 g/dL (0.1)	< 0.001
Indirect Bilirubin	-29.1% (3.5)	-2.8% (3.5)	< 0.001
Percent Reticulocyte Count	-18.0% (4.7)	6.8% (4.7)	< 0.001

QD = once daily; SE = standard error

Pediatric Patients 4 to < 12 years-

The efficacy and safety of Oxbryta® in patients 4 to <12 years with SCD was evaluated in an open-label, multi-center, Phase 2 trial [NCT 02850406]. In this study, 45 patients 4 to < 12 years and 11 patients 12 to <17 years received Oxbryta®. Patients 4 to <12 years received tablets for oral suspension based on body weight at baseline. Oxbryta® doses of 600 mg, 900 mg, or 1,500 mg once daily were administered to patients weighing 10 kg to < 20 kg, 20 kg to < 40 kg, or ≥40 kg, respectively. Patients 12 to < 17 years received Oxbryta® 1,500 mg once daily.

Patients were included if their baseline hemoglobin (Hb) was ≤10.5 g/dL. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. The trial excluded patients who had a VOC event within 14 days prior to enrollment, received red blood cell (RBC) transfusions within 30 days of enrollment, and had renal insufficiency or uncontrolled liver disease.

All patients had HbSS or HbS/beta0 -thalassemia genotype (100%) and most were receiving background hydroxyurea therapy (80%). The median age was 8 years (range: 4 to 15 years); 45 (80%) patients were 4 to < 12 years. In this age group, mean baseline Hb was 8.6 g/dL (range: 6.1 to 10.5 g/dL).

Efficacy was based on Hb response rate, which is defined as a Hb increase of > 1 g/dL from baseline to Week 24. Hb response rate for Oxbryta® in patients aged 4 to < 12 years who took at least one dose of Oxbryta® was 36% (16/45) (95% CI: 21.6%, 49.5%).