PDL DRUG REVIEW

Proprietary Name: Oxbryta®
Common Name: voxelotor
PDL Category: Sickle Cell Anemia Agents

Comparable Products	Preferred Drug List Status
Adakveo	Medical Coverage
Endari	Non-Preferred

Summary

Pharmacology/Usage: Voxelotor, the active ingredient of Oxbryta®, is a hemoglobin S (HbS) polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and has preferential partitioning to red blood cells. By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization. Non-clinical studies suggest that voxelotor may inhibit RBC sickling, improve RBC deformability, and reduce whole blood viscosity.

Indication: For the treatment of sickle cell disease (SCD) in adults and pediatric patients 12 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 trials.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There are adverse effects on maternal and fetal outcomes associated with SCD in pregnancy. Only use during pregnancy if the benefit of the drug outweighs the potential risk. The safety and efficacy of use in the pediatric population under the age of 12 years have not been established.

Dosage Form: Tablets: 500mg. Swallow tablets whole; do not cut, crush, or chew.

Recommended Dosage: Take 1,500mg PO QD, with or without food. Oxbryta® may be given with or without hydroxyurea.

Dose adjustments are not required with mild or moderate hepatic impairment; however, the recommended dosage with severe hepatic impairment is 1,000mg QD. Dose adjustments are not required with renal impairment; however, use has not been studied in patients with end stage renal disease requiring dialysis.

Drug Interactions: The concomitant use of strong CYP3A4 inhibitors or fluconazole may increase voxelotor plasma levels and may lead to increased toxicity. Avoid co-administration of Oxbryta® with strong CYP3A4 inhibitors or fluconazole and replace these drugs with alternative drugs when possible. If co-administration with a strong CYP3A4 inhibitor or fluconazole is unavoidable, the recommended Oxbryta® dose is 1,000mg QD.

The concomitant use of strong or moderate CYP3A4 inducers may decrease voxelotor plasma levels and may lead to reduced efficacy. Avoid the co-administration of Oxbryta® with strong or moderate CYP3A4 inducers. If co-administration with a strong or moderate CYP3A4 inducer is unavoidable, the recommended Oxbryta® dose is 2,500mg QD.

Voxelotor increased the systemic exposure of midazolam (a sensitive CYP3A4 substrate). Avoid the concomitant use of Oxbryta® with sensitive CYP3A4 substrates with a narrow therapeutic index. If concomitant use is unavoidable, consider dose reduction of the sensitive CYP3A4 substrate(s).

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Oxbryta®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included headache (4%), diarrhea (10%), abdominal pain (6%), nausea (7%), fatigue (4%), rash (4%), and pyrexia (5%).

Contraindications: In patients with a history of serious drug hypersensitivity reaction to voxelotor or excipients

Manufacturer: Global Blood Therapeutics

Analysis: The safety and efficacy of Oxbryta® in SCD were assessed in a randomized, double-blind, placebo-controlled multicenter study (HOPE) that included patients with 1 to 10 vaso-occlusive crisis (VOC) events within 12 months prior to enrollment and baseline hemoglobin (Hb) ≥5.5 to ≤ 10.5g/dl (N=274). Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea throughout the study. Furthermore, this trial excluded patients who received RBC transfusions within 60 days and erythropoietin within 28 days of enrollment, had renal insufficiency, uncontrolled liver disease, were pregnant, or lactating.

The median age of included patients was 24 years (range of 12 to 64 years), while 46 patients (17%) were 12 to <17 years of age. In addition, the median baseline Hb was 8.5g/dL, while 42% had 1 VOC event and 58% had 2 to 10 events within 12 months prior to enrollment.

Efficacy was based on Hb response rate, defined as a Hb increase of >1g/dL from baseline to week 24 in patients treated with Oxbryta® 1500mg as compared with placebo. Results suggested that the response rate for Oxbryta® was 51.1% (N=46/90) as compared to 6.5% (N=6/92) with placebo, which was significantly different (p<0.001). Additional efficacy outcomes included change in Hb and percent change in indirect bilirubin, as well as percent reticulocyte count from baseline to week 24. Results can be seen in the table below, which was adapted from the prescribing information.

	Oxbryta® 1,500mg QD (N=90)	Placebo (N=92)	p-value
Hemoglobin	1.14g/dL	-0.08g/dL	<0.001
Indirect Bilirubin	-29.08%	-3.16%	<0.001
% Reticulocyte Count	-19.93%	4.54%	<0.001

Place in Therapy: Oxbryta® is a hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease (SCD) in adults and 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). In one double-blind, placebo-controlled trial, patients on Oxbryta® had a significantly higher Hb response rate as compared those treated with placebo (NNT of 3).

It is recommended that Oxbryta® should be non-preferred and require prior authorization in order to confirm the appropriate diagnosis and clinical parameters for its use.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1]Oxbryta [package insert]. South San Francisco, CA: Global Blood Therapeutics; 2019.