SICKLE CELL DISEASE NEWS

Oxbryta (Voxelotor)

Oxbryta (voxelotor) is an oral therapy developed by Global Blood Therapeutics to treat sickle cell disease.

The treatment is approved by the U.S. Food and Drug Administration for people with sickle cell disease, and had been granted fast track, orphan drug, rare pediatric disease, and breakthrough therapy designations.

In addition, voxelotor has been included in the priority medicines (PRIME) program of the European Medicines Agency, and granted orphan drug designation by the European Commission for the treatment of sickle cell disease.

What is sickle cell disease?

Red blood cells contain a protein called hemoglobin that binds oxygen and enables its transport around the body. Sickle cell disease is caused by a mutation in the *HBB* gene that provides instructions for making a component of hemoglobin. The mutation results in the formation of an abnormal hemoglobin molecule called sickle hemoglobin or HbS.

HbS has a propensity to polymerize or stick together, forming long, rigid rods within red blood cells. This causes red blood cells to become stiff and elongated into a sickle or crescent shape instead of adopting their normally round and flexible shape. As a result, they cannot flow properly inside blood vessels, reducing oxygen delivery to different tissues in the body. These blockages can also cause inflammation and pain in what is called vaso-occlusive pain crises.

How does Oxbryta work?

Voxelotor, the active ingredient in Oxbryta, is a small molecule that binds to hemoglobin and increases the protein’s affinity for oxygen. By helping hemoglobin stay in the oxygenated state, Oxbryta also inhibits hemoglobin polymerization and

prevents red blood cells from becoming deformed. This should restore normal red blood cell function and oxygen delivery, reducing disease caused by the loss of red blood cells. It should also help reduce the risk of vaso-occlusive pain crises caused by sickle cells blocking small blood vessels.

Oxbryta in clinical trials

Oxbryta (formerly called GBT440) was evaluated in a randomized, placebo-controlled, double-blind Phase 1 clinical trial (NCT02285088), with a Phase 2 extension study (NCT03041909), which was completed in February 2018.

The studies assessed the safety, tolerability, pharmacokinetics (movement in the body), and pharmacodynamics (effect on the body) of Oxbryta in healthy volunteers and people with sickle cell disease.

The initial trial enrolled 133 participants who received Oxbryta or a placebo daily for up to 118 days, at a single site in London, England. Five patients then enrolled in the open-label extension study to continue receiving Oxbryta daily for up to six months.

The results of the trials, published in the journal *Blood*, showed an increase in hemoglobin with a profound and durable reduction in hemolysis (rupturing of red blood cells), and sickle cells in the blood. These findings, together with prior data, supported the safety and tolerability profile of Oxbryta.

A case report, published in the journal *Hematology Reports*, showed that Oxbryta treatment cleared jaundice — including scleral icterus where the eyes appear yellow — in one patient who completed both trials, markedly improving his quality of life.

A pivotal Phase 3 study called GBT_HOPE (NCT03036813) assessed the safety and efficacy of Oxbryta versus a placebo in patients with sickle cell disease. The results were published in the *New England Journal of Medicine*, and showed that Oxbryta significantly increased hemoglobin levels and reduced markers of hemolysis.

In this study, 274 patients with sickle cell disease, 12 or older, were randomly assigned to receive a placebo or once-daily Oxbryta at either 1,500 mg per day or 900 mg per day. After 24 weeks of treatment, 51.1% of patients receiving the higher dosage showed a significant increase in blood hemoglobin levels compared with 6.5% of the placebo group.

Based on the findings of this study, FDA approved Oxbryta in November of 2019 to treat sickle cell disease.

Other details

The most common adverse events associated with the use of Oxbryta are headaches, diarrhea, abdominal pain, fatigue, and nausea. No serious adverse events related to treatment have been reported.

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