FDA Approves Welireg for Cancers Associated With Von Hippel-Lindau Disease

Welirge (belzutifan) is approved for people who require therapy for associated renal cell carcinoma, central nervous system hemangioblastomas or pancreatic neuroendocrine tumors.

August 16, 2021 By Food and Drug Administration (FDA)

On August 13, 2021, the Food and Drug Administration approved belzutifan (Welireg, Merck), a hypoxia-inducible factor inhibitor for adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Belzutifan was investigated in the ongoing Study 004 (NCT03401788), an open-label clinical trial in 61 patients with VHL-associated RCC (VHL-RCC) diagnosed based on a VHL germline alteration and with at least one measurable solid tumor localized to the kidney. Enrolled patients had other VHL-associated tumors, including CNS hemangioblastomas and pNET. Patients received belzutifan 120 mg once daily until disease progression or unacceptable toxicity.

The primary efficacy endpoint was overall response rate (ORR) measured by radiology assessment, as assessed by an independent review committee using RECIST v1.1. Additional efficacy endpoints included duration of response (DoR), and time- to- response (TTR).

An ORR of 49% (95% CI:36, 62) was reported in patients with VHL-associated RCC. All patients with VHL-RCC with a response were followed for a minimum of 18 months from the start of treatment. The median DoR was not reached; 56% of responders had DoR ≥ 12 months and a median TTR of 8 months. In patients with other VHL-associated non-RCC tumors, 24 patients with measurable CNS hemangioblastomas had an ORR of 63% and 12 patients with measurable pNET had an ORR of 83%. Median DoR was not reached, with 73% and 50% of patients having response durations ≥ 12 months for CNS hemangioblastomas and pNET, respectively.

The most common adverse reactions, including laboratory abnormalities, reported in ≥ 20% of patients who received belzutifan were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea. Anemia and hypoxia from belzutifan use can be severe. In Study 004, anemia occurred in 90% of patients and 7% had Grade

3 anemia. Patients should be transfused as clinically indicated. The use of erythropoiesis stimulating agents for treatment of anemia is not recommended in patients treated with belzutifan. In Study 004, hypoxia occurred in 1.6% of patients. Belzutifan can render some hormonal contraceptives ineffective, and belzutifan exposure during pregnancy can cause embryo-fetal harm.

The recommended belzutifan dosage is 120 mg administered orally once daily with or without food.

View full prescribing information for Welireg.

This review was conducted under Project Orbis, an initiative of the FDA Oncology Center of Excellence. Project Orbis provides a framework for concurrent submission and review of oncology drugs among international partners. For this review, FDA collaborated with the Australian Therapeutic Goods Administration (TGA), Health Canada, and the Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom. The application reviews are ongoing at the other regulatory agencies.

This review used the Real-Time Oncology Review (RTOR) pilot program, which streamlined data submission prior to the filing of the entire clinical application, as well as the Assessment Aid and the Product Quality Assessment Aid, voluntary submissions from the applicant to facilitate the FDA's assessment. The FDA approved this application approximately 1 month ahead of the FDA goal date.

This application was granted priority review for this indication. A description of FDA expedited programs is in the Guidance for Industry: Expedited Programs for Serious Conditions-Drugs and Biologics.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's MedWatch Reporting System or by calling 1-800-FDA-1088.

This announcement was published by the Food and Drug Administration on August 13, 2021.
