BlueCross BlueShield
Federal Employee Program

WELIREG
(belzutifan)

RATIONALE FOR INCLUSION IN PA PROGRAM

Background

Welireg (belzutifan) is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that plays a role in the body's adaptation response to low oxygen levels. Under normal oxygen levels, HIF-2α is degraded by the von Hippel-Lindau (VHL) protein. Without functional VHL protein, the HIF-2α transcription factor accumulates, interacts with hypoxia-inducible factor 1 beta (HIF-1β) and leads to the expression of genes associated with cellular proliferation, angiogenesis, and tumor growth. Welireg inhibits the formation of the HIF-2α- HIF-1β complex, leading to reduced expression of downstream oncogenes (1).

Regulatory Status

FDA-approved indications: Welireg is a hypoxia-inducible factor inhibitor indicated: (1)

- For treatment of 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.
- For treatment of adult patients with advanced renal cell carcinoma (RCC) with a clear cell component following a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and a vascular endothelial growth factor tyrosine kinase inhibitor (VEGF-TKI).
- For treatment of adult and pediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL).

Welireg has a boxed warning regarding embryo-fetal toxicity. Exposure to Welireg during pregnancy can cause embryo-fetal harm and pregnancy status should be verified before initiation of treatment. Welireg can render some hormonal contraceptives ineffective. Female patients of reproductive potential and male patients with partners of reproductive potential should be advised to use effective non-hormonal contraception during treatment with Welireg and for 1 week after the last dose (1).

Welireg has warnings regarding anemia and hypoxia. Patients should be monitored for anemia before initiation and periodically throughout treatment. Welireg should be withheld until hemoglobin

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≥8g/dL, and then resumed at reduced dose or discontinued. Oxygen saturation should be monitored before initiating treatment and then periodically throughout treatment. If patient becomes hypoxic at rest, withhold Welireg until resolved, and then resume at reduced dose or discontinue permanently. In cases of life-threatening hypoxia, discontinue Welireg permanently (1).

The safety and effectiveness of Welireg in pediatric patients less than 12 years of age for the treatment of locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma have not been established. The safety and effectiveness of Welireg in pediatric patients less than 18 years of age for all other indications have not been established (1).

Summary

Welireg (belzutifan) is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α) and is indicated for von Hippel-Lindau (VHL) disease, advanced renal cell carcinoma (RCC), and locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma (PPGL). Welireg carries a boxed warning regarding embryo-fetal toxicity and patients should be advised to use to effective non-hormonal contraception. Welireg has also been shown to cause hypoxemia and anemia. Patients should be monitored for these conditions and dosage adjusted, or treatment discontinued as appropriate. The safety and effectiveness of Welireg in pediatric patients less than 12 years of age for the treatment of locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma have not been established. The safety and effectiveness of Welireg in pediatric patients less than 18 years of age for all other indications have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Welireg while maintaining optimal therapeutic outcomes.

References

1. Welireg [package insert]. Whitehouse Station, NJ: Merck Sharpe & Dohme Corp.; May 2025.
2. NCCN Drugs & Biologics Compendium® Belzutifan 2025. National Comprehensive Cancer Network, Inc. Accessed on May 15, 2025.