How well do you know **WELIREG**® (belzutifan)?

WELIREG is indicated for the 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).

WELIREG works differently by targeting HIF-2α, a key driver of tumor growth[1–3]

WHERE does WELIREG work?

WELIREG works in the nucleus.

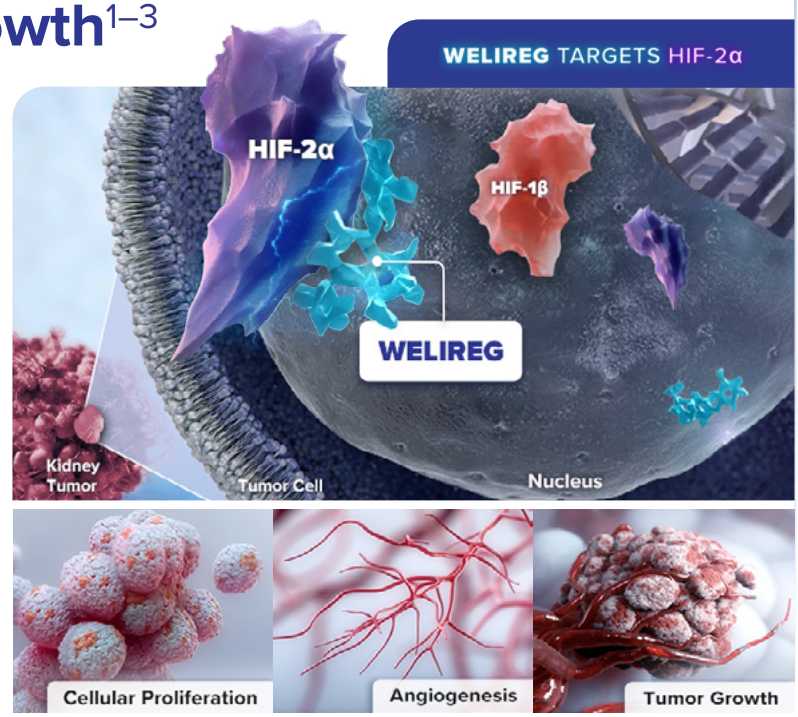
HOW does WELIREG work?

WELIREG binds to HIF-2α and, in conditions of hypoxia or impairment of VHL protein function, blocks HIF-2α–HIF-1β interaction.

This interaction may reduce the transcription and expression of HIF-2α target genes.

WHAT does WELIREG do?

When target genes are not expressed, associated downstream activities such as cellular proliferation, angiogenesis, and tumor growth may be reduced.



HIF-2α = hypoxia-inducible factor 2 alpha; HIF-1β = hypoxia factor 1 beta.

SELECTED SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY

- **Exposure to WELIREG during pregnancy can cause embryo-fetal harm.**
- **Verify pregnancy status prior to the initiation of WELIREG.**
- **Advise patients of these risks and the need for effective non-hormonal contraception as WELIREG can render some hormonal contraceptives ineffective.**

Anemia

- WELIREG can cause severe anemia that can require blood transfusion.
  - Monitor for anemia before initiation of, and periodically throughout, treatment. Transfuse patients as clinically indicated. For patients with hemoglobin <8 g/dL, withhold WELIREG until ≥8 g/dL, then resume at the same or reduced dose or permanently discontinue WELIREG, depending on the severity of anemia. For life-threatening anemia or when urgent intervention is indicated, withhold WELIREG until hemoglobin ≥8 g/dL, then resume at a reduced dose or permanently discontinue WELIREG.
- In LITESPARK-005 (n=372), decreased hemoglobin occurred in 88% of patients with advanced RCC with a clear cell component and 29% had Grade 3 events. Median time to onset of anemia was 29 days (range: 1 day to 16.6 months). Of the patients with anemia, 22% received transfusions only, 20% received erythropoiesis-stimulating agents (ESAs) only, and 12% received both transfusion and ESAs.

Selected Safety Information continues on the next page →

Before prescribing WELIREG, please read the additional Selected Safety Information on the next page and the accompanying Prescribing Information, including the Boxed Warning about embryo-fetal toxicity. The Medication Guide also is available.

WELIREG® (belzutifan) 40 mg tablets

FIRST IN CLASS

The approval of WELIREG marks the **first treatment option in a novel therapeutic class** available for your appropriate adult patients with 2L+ advanced clear cell RCC since 2015[3]

SCAN TO LEARN MORE

SELECTED SAFETY INFORMATION (*continued*)

Hypoxia

- WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization.
- Monitor oxygen saturation before initiation of, and periodically throughout, treatment. For decreased oxygen saturation with exercise (eg, pulse oximeter <88% or PaO_2 ≤55 mm Hg), consider withholding WELIREG until pulse oximetry with exercise is greater than 88%, then resume at the same or a reduced dose. For decreased oxygen saturation at rest (eg, pulse oximeter <88% or PaO_2 ≤55 mm Hg) or when urgent intervention is indicated, withhold WELIREG until resolved and resume at a reduced dose or discontinue. For life-threatening or recurrent symptomatic hypoxia, permanently discontinue WELIREG. Advise patients to report signs and symptoms of hypoxia immediately to a health care provider.
- In LITESPARK-005, hypoxia occurred in 15% of patients and 10% had Grade 3 events. Of the patients with hypoxia, 69% were treated with oxygen therapy. Median time to onset of hypoxia was 30.5 days (range: 1 day to 21.1 months).

Embryo-Fetal Toxicity

- Based on findings in animals, WELIREG can cause fetal harm when administered to a pregnant woman.
- Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. WELIREG can render some hormonal contraceptives ineffective. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Adverse Reactions

Adverse Reactions in LITESPARK-005

- Serious adverse reactions occurred in 38% of patients. The most frequently reported serious adverse reactions were hypoxia (7%), anemia (5%), pneumonia (3.5%), hemorrhage (3%), and pleural effusion (2.2%). Fatal adverse reactions occurred in 3.2% of patients who received WELIREG, including sepsis (0.5%) and hemorrhage (0.5%).
- WELIREG was permanently discontinued due to adverse reactions in 6% of patients. Adverse reactions which resulted in permanent discontinuation (≥0.5%) were hypoxia (1.1%), anemia (0.5%), and hemorrhage (0.5%).
- Dosage interruptions due to an adverse reaction occurred in 39% of patients. Of the patients who received WELIREG, 28% were 65 to 74 years, and 10% were 75 years and over. Dose interruptions occurred in 48% of patients ≥65 years of age and in 34% of younger patients. Adverse reactions which required dosage interruption in ≥2% of patients were anemia (8%), hypoxia (5%), COVID-19 (4.3%), fatigue (3.2%), and hemorrhage (2.2%).
- Dose reductions due to an adverse reaction occurred in 13% of patients. Dose reductions occurred in 18% of patients ≥65 years of age and in 10% of younger patients. The most frequently reported adverse reactions which required dose reduction (≥1.0%) were hypoxia (5%) and anemia (3.2%).
- The most common adverse reactions (≥25%), including laboratory abnormalities, were decreased hemoglobin (88%), fatigue (43%), musculoskeletal pain (34%), increased creatinine (34%), decreased lymphocytes (34%), increased alanine aminotransferase (32%), decreased sodium (31%), increased potassium (29%), and increased aspartate aminotransferase (27%).

Drug Interactions

- Coadministration of WELIREG with inhibitors of UGT2B17 or CYP2C19 increases plasma exposure of belzutifan, which may increase the incidence and severity of adverse reactions. Monitor for anemia and hypoxia and reduce the dosage of WELIREG as recommended.
- Coadministration of WELIREG with CYP3A4 substrates decreases concentrations of CYP3A4 substrates, which may reduce the efficacy of these substrates or lead to therapeutic failures. Avoid coadministration with sensitive CYP3A4 substrates. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information. Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding.

Lactation

- Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

Females and Males of Reproductive Potential

- WELIREG can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.
- Use of WELIREG may reduce the efficacy of hormonal contraceptives. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.
- Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential and the reversibility of this effect is unknown.

Renal Impairment

- For patients with severe renal impairment (eGFR 15-29 mL/min estimated by MDRD), monitor for increased adverse reactions and modify the dosage as recommended.

Hepatic Impairment

- For patients with moderate and severe hepatic impairment, monitor for increased adverse reactions and modify the dosage as recommended.

References: 1. Targeted drug therapy for kidney cancer. American Cancer Society. https://www.cancer.org/cancer/types/kidney-cancer/treating/targeted-therapy.html. Accessed June 12, 2025. **2.** Shenoy N, Pagliaro L. Sequential pathogenesis of metastatic VHL mutant clear cell renal cell carcinoma: putting it together with a translational perspective. *Ann Oncol.* 2016;27(9):1685–1695. **3.** Yap NY, Khoo WT, Perumal K, et al. Practical updates in medical therapy for advanced and metastatic renal cell carcinoma. *Urol Sci.* 2018;29(3):120–128.

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2L+ = second line or later.

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