
New Indication for Merck Product

Proprietary

Dear Members,

Merck would like to inform you that the FDA has approved WELIREG[®] (belzutifan) 40-mg tablets for the treatment of adult patients with advanced renal cell carcinoma (RCC) 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).

FDA=Food and Drug Administration.

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 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.

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 PaO₂ ≤ 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 PaO₂ ≤ 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).

Selected Safety Information continues below.

LITESPARK-005

- The efficacy of WELIREG was evaluated in LITESPARK-005, an open-label, randomized, active-controlled clinical trial in 746 patients with unresectable, locally advanced or metastatic clear cell RCC that progressed following PD-1 or PD-L1 checkpoint inhibitor and VEGF receptor targeted therapies either in sequence or in combination.
- Patients could have received up to 3 prior treatment regimens and were required to have measurable disease per RECIST v1.1. Patients were randomized in a 1:1 ratio to receive 120 mg WELIREG or 10 mg everolimus by oral administration once daily. Randomization was stratified by IMDC risk categories (favorable versus intermediate versus poor) and number of prior VEGF receptor targeted therapies (1 versus 2-3). Patients were evaluated radiologically at Week 9 from the date of randomization, then every 8 weeks through Week 49, and every 12 weeks thereafter.
- The study population characteristics were: median age 63 years [range 22 to 90 years], 42% age 65 or older; 78% male; 79% White; 12% Asian; 1% Black or African American; 11% Hispanic or Latino; 44% ECOG performance status 0 and 55% ECOG performance status 1. Prior therapies: 13% patients had 1 prior line of therapy, 43% had 2 prior lines of therapy and 43% had 3 prior lines of therapy; 49% received 2 to 3 prior VEGF receptor targeted therapies. Patient distribution by IMDC risk categories was 22% favorable, 66% intermediate, and 12% poor. Common sites of metastasis in patients were 65% lung, 59% lymph nodes, and 49% bone.
- The major efficacy endpoints were Progression Free Survival (PFS) measured by BICR using RECIST v1.1 and Overall Survival (OS). Additional efficacy endpoint included objective response rate (ORR) by BICR using RECIST v1.1.
- The trial demonstrated a statistically significant improvement in PFS for patients randomized to WELIREG compared with everolimus. The table below summarizes the efficacy results for LITESPARK-005.

Efficacy Results for Advanced RCC (IRC assessment) for LITESPARK-005

<u>Efficacy Outcome Measure</u>	<u>WELIREG</u> <u>n=374</u>	<u>Everolimus</u> <u>n=372</u>
<u>Progression-Free Survival (PFS)</u>		
<u>Number of events, n (%)</u>	<u>257 (69%)</u>	<u>262 (70%)</u>
<u>Progressive disease</u>	<u>234 (63%)</u>	<u>222 (60%)</u>
<u>Death</u>	<u>23 (6%)</u>	<u>40 (11%)</u>
<u>Median in months (95% CI)*</u>	<u>5.6 (3.9, 7.0)</u>	<u>5.6 (4.8, 5.8)</u>
<u>Hazard ratio[†] (95% CI)</u>	<u>0.75 (0.63, 0.90)</u>	
<u>p-Value[‡]</u>	<u>0.0008</u>	
<u>Confirmed Objective Response Rate</u>		
<u>Number of patients with measurable disease at baseline</u>	<u>373</u>	<u>364</u>
<u>ORR % (n) (95% CI)</u>	<u>22% (82)</u> <u>(18, 27)</u>	<u>4% (13)</u> <u>(2, 6)</u>
<u>Complete response</u>	<u>3% (10)</u>	<u>0% (0)</u>
<u>Partial response</u>	<u>19% (72)</u>	<u>4% (13)</u>
<u>p-Value[§]</u>	<u><0.0001</u>	

* From product-limit (Kaplan-Meier) method for censored data.

† Based on the stratified Cox proportional hazard model.

‡ One-sided p-Value based on stratified log-rank test compared with the significance boundary of 0.0021.

§ One-sided p-value based on stratified Miettinen and Nurminen (M&N) method.

- Among the 82 patients treated with WELIREG who achieved a confirmed response based on BICR per RECIST 1.1, 25 (30%) patients had a duration of response ≥ 12 months. OS results were immature. At the time of the subsequent pre-specified analysis, 59% of the patients had died in the randomized population.

BICR=blinded independent central review; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; IMDC=International Metastatic RCC Database Consortium; IRC=independent review committee; RECIST=Response Evaluation Criteria in Solid Tumors; VEGF=vascular endothelial growth factor.

Recommended Dosage for Patients With Advanced RCC Following a PD-1 or PD-L1 Inhibitor and a VEGF-TKI

- The recommended dosage of WELIREG is 120 mg administered orally once daily until disease progression or unacceptable toxicity. WELIREG should be taken at the same time each day and may be taken with or without food.
- Advise patients to swallow tablets whole. Do not chew, crush, or split WELIREG prior to swallowing.
- If a dose of WELIREG is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for WELIREG the next day. Do not take extra tablets to make up for the missed dose.
- If vomiting occurs any time after taking WELIREG, do not retake the dose. Take the next dose on the next day.

SELECTED SAFETY INFORMATION (*continued*)

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

- 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 ($\geq 0.5\%$) 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 $\geq 2\%$ 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 ($\geq 1.0\%$) were hypoxia (5%) and anemia (3.2%).
- The most common adverse reactions ($\geq 25\%$), 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.

Pediatric Use

- Safety and effectiveness of WELIREG in pediatric patients under 18 years of age have not been established.

Before prescribing WELIREG[®] (belzutifan), please read the accompanying [Prescribing Information](#), including the **Boxed Warning about embryo-fetal toxicity. The [Medication Guide](#) also is available.**

Sincerely,

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