FDA Approves Merck's WELIREG® (belzutifan) for the Treatment of Patients With Advanced Renal Cell Carcinoma (RCC) Following a PD-1 or PD-L1 Inhibitor and a VEGF-TKI

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First and only hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor approved for these adult patients with advanced RCC

This approval of WELIREG marks the first time a new treatment has been approved in a novel therapeutic class in advanced RCC since 2015

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved WELIREG, an oral hypoxia-inducible factor-2 alpha (HIF-2α) inhibitor, 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).

The approval is based on statistically significant and clinically meaningful results from LITESPARK-005, which is the only trial in advanced RCC to specifically evaluate patients who have progressed following a PD-1 or PD-L1 inhibitor and a VEGF-TKI. In the trial, WELIREG demonstrated superior progression-free survival (PFS) (HR=0.75 [95% CI, 0.63-0.90]; p=0.0008) versus everolimus in advanced RCC following treatment with both a PD-1 or PD-L1 checkpoint inhibitor and a VEGF receptor targeted therapy, given in sequence or in combination. Also, WELIREG showed an objective response rate (ORR) of 22% (n=82) (95% CI, 18-27) versus 4% (n=13) (95% CI, 2-6) for everolimus.
"Despite recent progress in the treatment of advanced RCC, there is yet to be an option specifically approved for patients whose disease progresses following a PD-1 or PD-L1 inhibitor and a TKI therapy," said Dr. Toni K. Choueiri, LITESPARK-005 study chair, director, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Jerome and Nancy Kohlberg professor of medicine, Harvard Medical School. "This approval of belzutifan introduces a meaningful new treatment option for certain patients, as belzutifan reduced the risk of disease progression or death compared to everolimus."

The WELIREG label contains a boxed warning that 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. WELIREG can cause severe anemia that can require a blood transfusion. Monitor for anemia before initiation of and periodically throughout treatment with WELIREG. WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization. Monitor oxygen saturation before initiation of and periodically throughout treatment with WELIREG. For more information, see “Selected Safety Information” below.

"In 2021, WELIREG became the first HIF-2α inhibitor therapy approved in the U.S. for the treatment of adult patients with certain VHL disease-associated tumors and is now approved for eligible patients with advanced RCC," said Dr. Marjorie Green, senior vice president and head of late-stage oncology, global clinical development, Merck Research Laboratories. "This approval of WELIREG marks the first new therapeutic class available for eligible patients with advanced RCC in nearly a decade, and was based on the statistically significant progression-free survival benefit observed in patients following treatment with a PD-1 or PD-L1 inhibitor and a VEGF-TKI when compared to everolimus."

Study design and additional data supporting the approval

The approval was based on data from LITESPARK-005, an open-label, randomized, active-controlled clinical trial (ClinicalTrials.gov, NCT04195750) 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 three prior treatment regimens and were required to have measurable disease per RECIST v1.1. Patients were randomized 1:1 to receive WELIREG (120 mg) (n=374) or everolimus (10 mg) (n=372) orally once daily. Randomization was stratified by the International Metastatic RCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and the 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 major efficacy endpoints were PFS as assessed by blinded independent central review (BICR) according to RECIST v1.1 and overall survival. Additional efficacy endpoints included ORR as assessed by BICR according to
The trial demonstrated a statistically significant improvement in PFS for patients randomized to WELIREG compared with everolimus.

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. Overall survival results were immature. At the time of the subsequent pre-specified analysis, 59% of the patients had died in the randomized population.

In the trial, WELIREG reduced the risk of disease progression or death by 25% (HR=0.75 [95% CI, 0.63-0.90]; p=0.0008) versus everolimus in these patients. Median PFS was 5.6 months (95% CI, 3.9-7.0) for WELIREG versus 5.6 months (95% CI, 4.8-5.8) for everolimus. The ORR for WELIREG was 22% (n=82) (95% CI, 18-27), with a complete response (CR) rate of 3% (n=10) and a partial response (PR) rate of 19% (n=72), and the ORR for everolimus was 4% (n=13) (95% CI, 2-6), with no patients achieving a CR and a PR rate of 4% (n=13).

The median duration of exposure was 7.6 months (range, 0.1 to 28.5 months) for WELIREG. Serious adverse reactions occurred in 38% of patients who received WELIREG. Serious adverse reactions in ≥2% of patients who received WELIREG 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 and hemorrhage (0.5% each). Permanent discontinuation of WELIREG due to adverse reactions occurred in 6% of patients. Adverse reactions that resulted in permanent discontinuation of WELIREG (≥0.5%) were hypoxia (1.1%), anemia and hemorrhage (0.5% each). Dosage interruptions of WELIREG due to an adverse reaction occurred in 39% of patients. Adverse reactions that 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 of WELIREG due to an adverse reaction occurred in 13% of patients. Adverse reactions that required dose reduction in ≥1% of patients were hypoxia (5%) and anemia (3.2%). The most common (≥25%) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin, fatigue, musculoskeletal pain, increased creatinine, decreased lymphocytes, increased alanine aminotransferase, decreased sodium, increased potassium, and increased aspartate aminotransferase. Clinically relevant adverse reactions in <10% of patients who received WELIREG in LITESPARK-005 included hemorrhage (9%) [including intracranial/cerebral hemorrhage (0.8%)], rash (8%), hypertension (6%), visual impairment [including vision blurred (4%), visual acuity decreased (1.1%), visual impairment (0.5%), and retinal detachment (0.3%)] (6%), and increased weight (5%).

About renal cell carcinoma

Renal cell carcinoma is by far the most common type of kidney cancer; about 9 out of 10 kidney cancer diagnoses are RCCs. Renal cell carcinoma is about twice as common in men than in women. Most cases of RCC are discovered...
incidentally during imaging tests for other abdominal diseases. Approximately 15% of patients with kidney cancer are diagnosed at an advanced stage.

About WELIREG® (belzutifan) 40 mg tablets, for oral use

Indications in the U.S.

Certain von Hippel-Lindau (VHL) disease-associated tumors

WELIREG (belzutifan) is indicated for the 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.

Advanced Renal Cell Carcinoma (RCC)

WELIREG is indicated 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).

Selected Safety Information for WELIREG

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-004 (N=61), decreased hemoglobin occurred in 93% of patients with VHL disease and 7% had Grade 3 events. Median time to onset of anemia was 31 days (range: 1 day to 8.4 months).
The use of erythropoiesis-stimulating agents (ESAs) for treatment of anemia is not recommended in patients with VHL disease who are treated with 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 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 (e.g., 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 (e.g., 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 healthcare provider.

In LITESPARK-004, hypoxia occurred in 1.6% of patients.

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**

In LITESPARK-004, serious adverse reactions occurred in 15% of patients, including anemia, hypoxia, anaphylaxis
reaction, retinal detachment, and central retinal vein occlusion (1 patient each).

WELIREG was permanently discontinued due to adverse reactions in 3.3% of patients for dizziness and opioid overdose (1.6% each).

Dosage interruptions due to an adverse reaction occurred in 39% of patients. Those which required dosage interruption in >2% of patients were fatigue, decreased hemoglobin, anemia, nausea, abdominal pain, headache, and influenza-like illness.

Dose reductions due to an adverse reaction occurred in 13% of patients. The most frequently reported adverse reaction which required dose reduction was fatigue (7%).

The most common adverse reactions (≥25%), including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin (93%), fatigue (64%), increased creatinine (64%), headache (39%), dizziness (38%), increased glucose (34%), and nausea (31%).

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%) and hemorrhage (0.5%).

Dosage interruptions due to an adverse reaction occurred in 39% of 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. The most frequently reported adverse reactions which required dose reduction (≥1.0%) were hypoxia (5%) and anemia (3.2%).

The most common (≥25%) adverse reactions, including laboratory abnormalities, were decreased hemoglobin (88%), fatigue (43%), musculoskeletal pain (33%), 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.

**Merck’s focus on cancer**

Our goal is to translate breakthrough science into innovative oncology medicines to help people with cancer worldwide. At Merck, the potential to bring new hope to people with cancer drives our purpose and supporting accessibility to our cancer medicines is our commitment. As part of our focus on cancer, Merck is committed to
exploring the potential of immuno-oncology with one of the largest development programs in the industry across more than 30 tumor types. We also continue to strengthen our portfolio through strategic acquisitions and are prioritizing the development of several promising oncology candidates with the potential to improve the treatment of advanced cancers. For more information about our oncology clinical trials, visit www.merck.com/clinicaltrials.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. For more information, visit www.merck.com and connect with us on X (formerly Twitter), Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Rahway, N.J., USA

This news release of Merck & Co., Inc., Rahway, N.J., USA (the “company”) includes “forward-looking statements” within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company’s management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline candidates that the candidates will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of the global outbreak of novel coronavirus disease (COVID-19); the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company’s patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of
new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's Annual Report on Form 10-K for the year ended December 31, 2022 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).


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