

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215383Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use WELIREG safely and effectively. See full prescribing information for WELIREG.

WELIREG™ (belzutifan) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

- 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 render some hormonal contraceptives ineffective. (5.3, 7.2, 8.1, 8.3)

INDICATIONS AND USAGE

WELIREG is a hypoxia-inducible factor inhibitor indicated 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. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage of WELIREG is 120 mg administered orally once daily with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- **Anemia:** Monitor for anemia before initiation of and periodically throughout treatment with WELIREG. Withhold WELIREG until hemoglobin ≥ 9 g/dL, then resume at reduced dose or discontinue. For life threatening anemia, or for anemia requiring urgent intervention, withhold WELIREG until hemoglobin ≥ 9 g/dL and resume at a reduced dose or permanently discontinue WELIREG. (2.2, 5.1)
- **Hypoxia:** Monitor oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG. For hypoxia at rest, withhold until resolved, resume at reduced dose, or discontinue depending on severity. For life-threatening hypoxia, permanently discontinue WELIREG. (2.2, 5.2)

ADVERSE REACTIONS

Most common ($\geq 25\%$) adverse reactions, including laboratory abnormalities, were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

UGT2B17 or CYP2C19 Inhibitors: Monitor for signs and symptoms of anemia and hypoxia and reduce the dosage of WELIREG as recommended. (2.2, 7.1)

USE IN SPECIFIC POPULATIONS

- **Lactation:** Advise not to breastfeed. (8.2)
- **Infertility:** May impair fertility in males and females. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING 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. WELIREG can render some hormonal contraceptives ineffective [see *Warnings and Precautions (5.3), Drug Interactions (7.2), Use in Specific Populations (8.1, 8.3)*].

1 INDICATIONS AND USAGE

WELIREG is indicated 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

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.

2.2 Dosage Modifications for Adverse Reactions

Dosage modifications for WELIREG for adverse reactions are summarized in Table 1.

The recommended dose reductions are:

- First dose reduction: WELIREG 80 mg orally once daily
- Second dose reduction: WELIREG 40 mg orally once daily
- Third dose reduction: Permanently discontinue

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity	Dosage Modification
Anemia [see <i>Warnings and Precautions (5.1)</i>]	Hemoglobin <9 g/dL or transfusion indicated	• Withhold until hemoglobin $\geq$9g/dL. • Resume at reduced dose or discontinue depending on the severity of anemia.
	Life-threatening or urgent intervention indicated	• Withhold until hemoglobin $\geq$9g/dL. • Resume at a reduced dose or permanently discontinue.
Hypoxia [see <i>Warnings and Precautions (5.2)</i>]	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%)	• Consider withholding until resolved. • Resume at the same dose or at a reduced dose depending on the severity of hypoxia.
	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO ₂ $\leq$ 55 mm Hg) or urgent intervention indicated	• Withhold until resolved. • Resume at reduced dose or discontinue depending on the severity of hypoxia.

	Life-threatening or recurrent symptomatic hypoxia	Permanently discontinue.
Other Adverse Reactions [see Adverse Reactions (6)]	Grade 3	- Withhold dosing until resolved to ≤ Grade 2. - Consider resuming at a reduced dose (reduce by 40 mg). - Permanently discontinue upon recurrence of Grade 3.
	Grade 4	Permanently discontinue.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg, blue, oval shaped, film-coated, debossed with “177” on one side and plain on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anemia

WELIREG can cause severe anemia that can require blood transfusion.

In Study 004, anemia occurred in 90% of patients and 7% had Grade 3 anemia [see Adverse Reactions (6.1)]. Median time to onset of anemia was 31 days (range: 1 day to 8.4 months). In another clinical trial [Study 001 (n=58)] in patients with advanced solid tumors who received the same dosage of WELIREG, anemia occurred in 76% of patients and 28% had Grade 3 anemia.

Monitor for anemia before initiation of, and periodically throughout, treatment with WELIREG. Closely monitor patients who are dual UGT2B17 and CYP2C19 poor metabolizers due to potential increases in exposure that may increase the incidence or severity of anemia [see Clinical Pharmacology (12.5)].

Transfuse patients as clinically indicated. For patients with hemoglobin <9g/dL, withhold WELIREG until ≥9g/dL, then resume at 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 ≥9g/dL, then resume at a reduced dose or permanently discontinue WELIREG [see Dosage and Administration (2.2)].

The use of erythropoiesis stimulating agents (ESAs) for treatment of anemia is not recommended in patients treated with WELIREG. For patients treated with WELIREG who develop anemia, the safety and effectiveness for use of ESAs have not been established. Randomized controlled trials in patients with cancer receiving myelosuppressive chemotherapy with ESAs have shown that ESAs increased the risks of death and serious cardiovascular reactions, and decreased progression-free survival and/or overall survival. See the prescribing information for ESAs for more information.

5.2 Hypoxia

WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization [see Dosage and Administration (2.2)].

In Study 004, hypoxia occurred in 1.6% of patients [see Adverse Reactions (6.1)]. In another clinical trial [Study 001 (n=58)] in patients with advanced solid tumors who received the same dosage of WELIREG, hypoxia occurred in 29% of patients, including Grade 3 hypoxia in 16%.

Monitor oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG. 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 dose or at a reduced dose. For decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO₂ ≤55 mm Hg) or urgent intervention indicated, withhold WELIREG until resolved and resume at a reduced

dose or discontinue. For life-threatening hypoxia or for recurrent symptomatic hypoxia, permanently discontinue WELIREG [see *Dosage and Administration* (2.2)].

Advise patients to report signs and symptoms of hypoxia immediately to a healthcare provider.

5.3 Embryo-Fetal Toxicity

Based on findings in animals, WELIREG can cause fetal harm when administered to a pregnant woman. In an animal reproduction study, oral administration of belzutifan to pregnant rats during the period of organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations at maternal exposures ≥ 0.2 times the human exposures (AUC) at the recommended dose of 120 mg daily.

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, since WELIREG can render some hormonal contraceptives ineffective [see *Drug Interactions* (7.1)]. 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 [see *Use in Specific Populations* (8.1, 8.3)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Anemia [see *Warnings and Precautions* (5.1)]
- Hypoxia [see *Warnings and Precautions* (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of WELIREG was evaluated in an open-label clinical trial (Study 004) in 61 patients with VHL disease who had at least one measurable solid tumor localized to the kidney [see *Clinical Studies* (14)]. Patients received WELIREG 120 mg orally once daily. The median duration of exposure to WELIREG was 68 weeks (range: 8.4 to 104.7 weeks).

Serious adverse reactions occurred in 15% of patients who received WELIREG, including anemia, hypoxia, anaphylaxis reaction, retinal detachment, and central retinal vein occlusion (1 patient each).

Permanent discontinuation of WELIREG due to adverse reactions occurred in 3.3% of patients. Adverse reactions which resulted in permanent discontinuation of WELIREG were dizziness and opioid overdose (1.6% each).

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

Dose reductions of WELIREG 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 ($\geq 25\%$) adverse reactions, including laboratory abnormalities, that occurred in patients who received WELIREG were decreased hemoglobin, anemia, fatigue, increased creatinine, headache, dizziness, increased glucose, and nausea.

Table 2 summarizes the adverse reactions reported in patients treated with WELIREG in Study 004.

Table 2: Adverse Reactions Occurring in $\geq 10\%$ of Patients Who Received WELIREG in Study 004

Adverse Reaction	WELIREG N=61
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	All Grades* (%)	Grade 3-4 (%)
Blood and Lymphatic		
Anemia	90	7
General		
Fatigue [†]	64	5
Nervous system		
Headache [‡]	39	0
Dizziness [§]	38	0
Gastrointestinal		
Nausea	31	0
Constipation	13	0
Abdominal pain [¶]	13	0
Eye Disorders		
Visual impairment [#]	21	3.3
Infections		
Upper respiratory tract infection ^p	21	0
Respiratory, Thoracic and Mediastinal		
Dyspnea	20	1.6
Musculoskeletal and Connective Tissue		
Arthralgia	18	0
Myalgia	16	0
Vascular		
Hypertension	13	3.3
Metabolism and Nutrition		
Weight increased	12	1.6

*Graded per NCI CTCAE v4.0

[†] includes fatigue and asthenia

[‡] includes headache and migraine

[§] includes dizziness and vertigo

[¶] includes abdominal discomfort, abdominal pain, abdominal pain upper and abdominal pain lower

[#] includes visual impairment, vision blurred, central retinal vein occlusion and retinal detachment

includes bronchitis, sinusitis, upper respiratory tract infection, and viral upper respiratory infection

Table 3 summarizes the laboratory abnormalities in Study 004.

Table 3: Select Laboratory Abnormalities ($\geq 10\%$) That Worsened from Baseline in Patients Who Received WELIREG in Study 004

Laboratory Abnormality*	WELIREG (n=61)	
	Grades 1-4 %	Grades 3-4 %
Chemistry		
Increased creatinine	64	0
Increased glucose	34	4.9
Increased ALT	20	0
Increased AST	16	0
Decreased calcium (corrected)	10	0
Decreased phosphate	10	1.6
Hematology		
Decreased hemoglobin	93	7
Decreased leukocytes	11	0

*The denominator used to calculate the rate is based on all patients in the safety analysis population.

Other Clinical Trials Experience

In Study 001 (NCT02974738), a clinical trial in patients with advanced solid tumors (n=58) treated at the recommended dose in which the median age of enrollment was 62.5 years (range 39-75) and the median number of prior therapies for cancer was 3 (range 1-9), the following additional adverse reactions have been reported following administration of WELIREG at the recommended dosage: edema, cough, musculoskeletal pain, vomiting, diarrhea, and dehydration.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on WELIREG

UGT2B17 or CYP2C19 Inhibitors

Coadministration of WELIREG with inhibitors of UGT2B17 or CYP2C19 increases plasma exposure of belzutifan [see *Clinical Pharmacology* (12.3, 12.5)], which may increase the incidence and severity of adverse reactions of WELIREG. Monitor for anemia and hypoxia and reduce the dosage of WELIREG as recommended [see *Dosage and Administration* (2.2), *Warnings and Precautions* (5.1, 5.2), *Adverse Reactions* (6)].

7.2 Effect of WELIREG on Other Drugs

Sensitive CYP3A4 Substrates

Coadministration of WELIREG with CYP3A4 substrates decreases concentrations of CYP3A substrates [see *Clinical Pharmacology* (12.3)], which may reduce the efficacy of these substrates. The magnitude of this decrease may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolizers [see *Clinical Pharmacology* (12.3)]. Avoid coadministration of WELIREG with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information.

Hormonal Contraceptives

Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding [see *Clinical Pharmacology* (12.3), *Use in Specific Populations* (8.3)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies, WELIREG can cause fetal harm when administered to a pregnant woman. There are no available data on the use of WELIREG in pregnant women to inform the drug-associated risk. In an animal reproduction study, oral administration of belzutifan to pregnant rats during the period of organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal malformations at maternal exposures ≥ 0.2 times the human exposure (AUC) at the recommended dose of 120 mg daily (*see Data*). Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Data

Animal Data

In a pilot embryo-fetal development study, pregnant rats received oral doses of 6, 60, or 200 mg/kg/day of belzutifan during the period of organogenesis. Belzutifan caused embryo-fetal lethality at doses ≥ 60 mg/kg/day (approximately 1 time the human exposure at the recommended dose based on AUC). Reduced fetal body weights, fetal rib malformations, and reduced skeletal ossification occurred at doses of 6 and 60 mg/kg/day (approximately ≥ 0.2 times the human exposure at the recommended dose based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of belzutifan or its metabolites in human milk or their effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

WELIREG can cause fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.

Contraception

Females

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 [*see Drug Interactions (7.2)*].

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with WELIREG and for 1 week after the last dose.

Infertility

Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential [*see Nonclinical Toxicology (13.1)*]. The reversibility of the effect on fertility is unknown.

8.4 Pediatric Use

Safety and effectiveness of WELIREG have not been established in pediatric patients.

8.5 Geriatric Use

Of the patients who received WELIREG in Study 004, 3.3% were ≥ 65 years old [see *Clinical Studies (14)*]. Clinical trials of WELIREG did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

8.6 Renal Impairment

No dosage modification of WELIREG is recommended in patients with mild (eGFR 60-89 mL/min/1.73 m² estimated by MDRD) and moderate (eGFR 30-59 mL/min/1.73 m²) renal impairment [see *Clinical Pharmacology (12.3)*]. WELIREG has not been studied in patients with severe (eGFR 15-29 mL/min/1.73 m²) renal impairment.

8.7 Hepatic Impairment

No dosage modification of WELIREG is recommended in patients with mild [total bilirubin $\leq$ upper limit of normal (ULN) and aspartate aminotransferase (AST) $>$ ULN or total bilirubin >1 to $1.5 \times$ ULN and any AST] hepatic impairment. WELIREG has not been studied in patients with moderate or severe hepatic impairment (total bilirubin $>1.5 \times$ ULN and any AST) [see *Clinical Pharmacology (12.3)*].

8.8 Dual UGT2B17 and CYP2C19 Poor Metabolizers

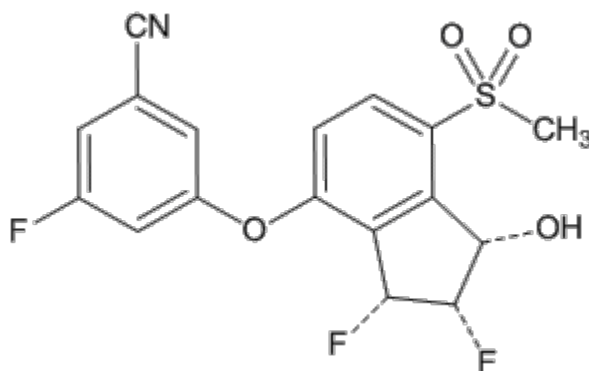
Patients who are dual UGT2B17 and CYP2C19 poor metabolizers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of WELIREG. Closely monitor for adverse reactions in patients who are dual UGT2B17 and CYP2C19 poor metabolizers [see *Warnings and Precautions (5)*, *Adverse Reactions (6)*, *Clinical Pharmacology (12.5)*].

10 OVERDOSAGE

There is no specific treatment for WELIREG overdose. In cases of suspected overdose, withhold WELIREG and institute supportive care. Grade 3 hypoxia occurred at dosages of 120 mg twice a day and Grade 4 thrombocytopenia occurred at dosages of 240 mg once daily (approximately 2 times the recommended dosage).

11 DESCRIPTION

Belzutifan is an inhibitor of hypoxia-inducible factor-2 α (HIF-2 α). The chemical name of belzutifan is 3-[[[(1S,2S,3R)-2,3-Difluoro-2,3-dihydro-1-hydroxy-7-(methylsulfonyl)-1H-inden-4-yl]oxy]-5-fluorobenzonitrile. The molecular formula is C₁₇H₁₂F₃NO₄S and the molecular weight is 383.34 Daltons. The chemical structure is:



Belzutifan is a white to light brown powder that is soluble in acetonitrile, dimethoxyethane, and acetone, sparingly soluble in ethyl acetate, very slightly soluble in isopropanol and toluene, and insoluble in water.

WELIREG is supplied as blue, film-coated tablets for oral use containing 40 mg of belzutifan together with croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide, as inactive ingredients. In addition, the film-coating contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2 α). HIF-2 α is a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2 α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilization and accumulation of HIF-2 α . Upon stabilization, HIF-2 α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1 β) to form a transcriptional complex that induces expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2 α , and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2 α -HIF-1 β interaction, leading to reduced transcription and expression of HIF-2 α target genes. In vivo, belzutifan demonstrated anti-tumor activity in mouse xenograft models of renal cell carcinoma.

12.2 Pharmacodynamics

Reductions in plasma levels of erythropoietin (EPO) were observed to be dose- and exposure-dependent at dosages up to 120 mg once daily. The maximum EPO suppression occurred following 2 weeks of consecutive dosing of WELIREG (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

The incidence of Grade 3 anemia increased with higher belzutifan exposure in patients with baseline hemoglobin levels <12 mg/dL [see *Warnings and Precautions* (5.1)].

Cardiac Electrophysiology

At the recommended dosage, WELIREG does not cause large mean increases (i.e., >20 msec) in the QT interval.

12.3 Pharmacokinetics

The mean steady-state (CV%) C_{max} is 1.3 μ g/mL (42%) and AUC_{0-24h} is 16.7 μ g•hr/mL (52%) in patients with VHL disease-associated RCC. Steady state is reached after approximately 3 days. C_{max} and AUC increase proportionally over a dose range of 20 mg to 120 mg (0.17 to 1 times the approved recommended dose).

Absorption

The median T_{max} occurs at 1 to 2 hours after administration.

Effect of Food

A high-fat, high-calorie meal (total calories approximately 1000 kcal, 56 g fat, 55 g carbohydrate, and 31 g protein) delayed time to reach peak belzutifan concentration by approximately 2 hours, had no clinically meaningful effect on C_{max} , and had no effect on AUC.

Distribution

The mean (CV%) steady-state volume of distribution is 130 L (35%). Plasma protein binding of belzutifan is 45%. The blood-to-plasma concentration ratio of belzutifan is 0.88.

Elimination

The mean (CV%) clearance is 7.3 L/hr (51%) and the mean elimination half-life is 14 hrs.

Metabolism

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4 [see *Clinical Pharmacology* (12.5)].

Specific Populations

Patients who are poor metabolizers of UGT2B17 and CYP2C19 had higher belzutifan AUC [see *Clinical Pharmacology* (12.5)].

There were no clinically significant differences in the pharmacokinetics of belzutifan based on age (19 to 84 years), sex, ethnicity (non-Hispanic, Hispanic), race (White, Black, Asian, Pacific Islander), body weight (42 to 166 kg), mild to moderate renal impairment (eGFR 30-89 mL/min/1.73 m² estimated by MDRD), or mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN or total bilirubin > ULN to 1.5 x ULN with any AST). The effect of severe renal impairment (eGFR 15-29 mL/min/1.73 m²) and moderate to severe hepatic impairment (total bilirubin > 1.5 x ULN and any AST) have not been studied.

Drug Interaction Studies

Clinical Studies and Model-Informed Approaches

Effect of Belzutifan on CYP3A Substrates: Coadministration of WELIREG 120 mg once daily with midazolam (a sensitive CYP3A4 substrate) decreased the midazolam AUC by 40% and the C_{max} by 34%. Midazolam AUC is predicted to decrease up to 70% in patients with higher belzutifan concentrations (e.g., dual poor metabolizers) [see *Clinical Pharmacology* (12.5)].

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Belzutifan does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

Belzutifan does not induce CYP1A2 or CYP2B6.

Transporter Systems: Belzutifan is a substrate of P-gp, OATP1B1, and OATP1B3, but is not a substrate of BCRP.

Belzutifan inhibits MATE2K. Belzutifan does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or MATE1.

12.5 Pharmacogenomics

Patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers have 2-, 1.6-, or 3.2-fold higher belzutifan steady state AUC_{0-24h} (respectively) compared to patients who are UGT2B17 normal (extensive) metabolizers and CYP2C19 non-poor (ultrarapid, rapid, normal, and intermediate) metabolizers [see *Use in Specific Populations* (8.7)].

UGT2B17 poor metabolizers who are homozygous for the UGT2B17*2 allele have no UGT2B17 enzyme activity. CYP2C19 poor metabolizers (such as *2/*2, *3/*3, *2/*3) have significantly reduced or absent CYP2C19 enzyme activity. Approximately 15% of White, 6% of Black or African American, and up to 77% of certain Asian populations are UGT2B17 poor metabolizers. Approximately 2% of White, 5% of Black or African American, and up to 19% of certain Asian populations are CYP2C19 poor metabolizers. Approximately 0.4% of White, 0.3% of Black or African American, and up to 15% of certain Asian populations are dual UGT2B17 and CYP2C19 poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with belzutifan.

Belzutifan was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay. Belzutifan was not clastogenic in either an in vitro micronucleus assay or an in vivo rat bone marrow micronucleus assay.

Fertility studies in animals have not been conducted with belzutifan. In repeat-dose toxicity studies up to 3-month duration, belzutifan-related findings included degeneration/atrophy of testes and hypospermia and cellular debris of the epididymis in rats administered ≥2 mg/kg/day (approximately 0.1 times the human exposure at the recommended dose of 120 mg daily). Findings in testes and epididymis were associated with decreased sperm count and motility and abnormal sperm morphology at ≥6 mg/kg/day (approximately 0.2 times the human exposure at the recommended dose of 120 mg daily) and did not

reverse by the end of the recovery period. Belzutifan had no adverse effects on female reproductive organs in repeat-dose toxicity studies up to 3-month duration; however, belzutifan caused embryo-fetal lethality (post-implantation loss) in pregnant rats given oral doses ≥ 60 mg/kg/day (approximately 1 time the human exposure at the recommended dose based on AUC) during the period of organogenesis [see *Use in Specific Population (8.1)*].

14 CLINICAL STUDIES

The efficacy of WELIREG was evaluated in Study 004 (NCT03401788), an open-label clinical trial in 61 patients with VHL-associated RCC diagnosed based on a VHL germline alteration and with at least one measurable solid tumor localized to the kidney as defined by response evaluation criteria in solid tumors (RECIST) v1.1. Enrolled patients had other VHL-associated tumors including CNS hemangioblastomas and pNET. CNS hemangioblastomas and pNET in these patients were diagnosed based on the presence of at least one measurable solid tumor in brain/spine or pancreas, respectively, as defined by RECIST v1.1 and identified by IRC. The study excluded patients with metastatic disease. Patients received WELIREG 120 mg once daily until progression of disease or unacceptable toxicity.

The study population characteristics were: median age 41 years [range 19-66 years], 3.3% age 65 or older; 53% male; 90% were White, 3.3% were Black or African-American, 1.6% were Asian, and 1.6% were Native Hawaiian or other Pacific Islander; 82% had an ECOG PS of 0, 16% had an ECOG PS of 1, and 1.6% had an ECOG PS of 2; and 84% had VHL Type I Disease. The median diameter of RCC target lesions per central independent review committee (IRC) was 2.2 cm (range 1-6.1). Median time from initial radiographic diagnosis of VHL-associated RCC tumors that led to enrollment on Study 004 to the time of treatment with WELIREG was 17.9 months (range 2.8-96.7). Seventy-seven percent of patients had prior surgical procedures for RCC.

The major efficacy endpoint for the treatment of VHL-associated RCC was overall response rate (ORR) measured by radiology assessment using RECIST v1.1 as assessed by IRC. Additional efficacy endpoints included duration of response (DoR), and time to response (TTR).

Table 4 summarizes the efficacy results for VHL-associated RCC in Study 004.

Table 4: Efficacy Results (IRC assessment) for WELIREG for VHL-Associated RCC

Efficacy Outcome Measure	WELIREG n=61
Overall Response Rate, % (n) (95% CI)	49% (30)* (36, 62)
Complete response	0%
Partial response	49%
Duration of Response	
Median in months (range)	Not reached (2.8+, 22+)
% (n) with DoR $\geq$ 12 months	56% (17/30)

* All patients with a response were followed for a minimum of 18 months from the start of treatment.

+ Denotes ongoing response.

For VHL-associated RCC, median TTR was 8 months (range 2.7, 19).

Table 5 summarizes the efficacy results for VHL-associated pNET or CNS hemangioblastomas in Study 004.

Table 5. Efficacy Results (IRC assessment) for WELIREG for VHL-Associated Subgroups with CNS Hemangioblastomas or pNET

Endpoint	Patients with CNS Hemangioblastomas n=24*	Patients with pNET n=12*
Overall Response Rate, % (n) (95% CI)	63%, (15) (41, 81)	83% (10) (52, 98)
Complete response	4% (1)	17% (2)
Partial response	58% (14)	67% (8)
Duration of Response		
Median in months (range)	Not reached (3.7+, 22+)	Not reached (11+, 19+)
% (n) with DoR ≥12 months	73% (11/15)	50% (5/10)

* Number of patients with measurable solid lesions, based on IRC assessment.

+ Denotes ongoing response.

For VHL-associated CNS hemangioblastomas, TTR was 3.1 months (range 2.5, 11). For VHL-associated pNET, median TTR was 8.1 months (range 2.7, 11).

Decreases in size of CNS hemangioblastoma-associated peri-tumoral cysts and syringes were observed.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

WELIREG tablets are supplied as 40 mg blue, oval shaped, film-coated, debossed with “177” on one side and plain on the other side, available in:

- bottles of 90 tablets with child-resistant closure: NDC 0006-5331-01.

The bottle also contains two desiccant canisters. Do not eat.

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anemia

Inform patients that WELIREG can cause severe anemia that may require blood transfusions and that red blood cell levels will be monitored routinely during treatment. Advise patients to contact their healthcare provider if the patient experiences any symptoms suggestive of anemia [see *Warnings and Precautions* (5.1)].

Hypoxia

Inform patients that WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization; and that oxygen levels will be monitored routinely during treatment. Advise patients to contact their healthcare provider if the patient experiences any symptoms suggestive of hypoxia [see *Warnings and Precautions* (5.2)].

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential of the risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.3) and *Use in Specific Population* (8.1)].

- Advise females of reproductive potential to use effective non-hormonal contraception during treatment with WELIREG and for 1 week after the last dose [see *Use in Specific Populations* (8.3)].
- 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 [see *Use in Specific Populations* (8.3)].

Lactation

Advise females not to breastfeed during treatment with WELIREG and for 1 week after the last dose [see *Use in Specific Populations* (8.2)].

Infertility

Advise male and female patients that WELIREG may impair fertility [see *Use in Specific Populations* (8.3)].

Dosage and Administration

Instruct patients to take their dose of WELIREG at the same time each day (once daily). Advise patients WELIREG can be taken with or without food. Each tablet should be swallowed whole [see *Dosage and Administration* (2.1)].

 Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

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MEDICATION GUIDE
WELIREG™ (Well-ih-reg)
(belzutifan)
tablets

What is the most important information I should know about WELIREG?

WELIREG may cause serious side effects, including:

- **Low red blood cell counts (anemia).** Low red blood cell counts are common with WELIREG and can be severe. You may need a blood transfusion if your red blood cell counts drop too low. Your healthcare provider will do blood tests to check your red blood cell counts before you start and during treatment with WELIREG. Tell your healthcare provider if you get any symptoms of low red blood cell counts, including tiredness, feeling cold, shortness of breath, chest pain, or fast heartbeat.
- **Low oxygen levels in your body.** WELIREG can cause low oxygen levels in your body that can be severe and may require you to stop treatment with WELIREG, receive oxygen therapy, or be hospitalized. Your healthcare provider will monitor your oxygen levels before you start and during treatment with WELIREG. Tell your healthcare provider or get medical help right away if you get symptoms of low oxygen in your body, including shortness of breath or increased heart rate.
- **Harm to your unborn baby.** Treatment with WELIREG during pregnancy can cause harm to your unborn baby.

Females who are able to become pregnant:

- o Your healthcare provider will do a pregnancy test before you start treatment with WELIREG.
- o You should use an effective form of non-hormonal birth control (contraception) during treatment with WELIREG and **for 1 week** after your last dose.
- o Birth control methods that contain hormones (such as birth control pills, injections, or transdermal system patches) may not work as well during treatment with WELIREG.
- o Talk to your healthcare provider about birth control methods that may be right for you during treatment with WELIREG.
- o Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with WELIREG.

Males with female partners who are able to become pregnant:

- o You should use effective birth control (contraception) during treatment with WELIREG and **for 1 week** after your last dose.
- o Tell your healthcare provider right away if your partner becomes pregnant or thinks she is pregnant while you are taking WELIREG.

See “**What are the possible side effects of WELIREG?**” for more information about side effects.

What is WELIREG?

WELIREG is a prescription medicine used to treat adults with von Hippel-Lindau (VHL) disease who need treatment for a type of kidney cancer called renal cell carcinoma (RCC), tumors in the brain and spinal cord called central nervous system hemangioblastomas, or a type of pancreatic cancer called pancreatic neuroendocrine tumors, that do not require surgery right away.

It is not known if WELIREG is safe and effective in children.

Before taking WELIREG, tell your healthcare provider about all of your medical conditions, including if you:

- have low red blood cell counts (anemia)
- are pregnant or plan to become pregnant. See “**What is the most important information I should know about WELIREG?**”
- are breastfeeding or plan to breastfeed. It is not known if WELIREG passes into your breast milk. **Do not** breastfeed during treatment with WELIREG and for 1 week after your last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. WELIREG and certain other medicines can affect each other and cause serious side effects.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take WELIREG?

- Take WELIREG exactly as your healthcare provider tells you.
- Do not stop taking WELIREG or change your dose without talking to your healthcare provider.
- Take your prescribed dose of WELIREG 1 time a day, at the same time each day.
- Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with WELIREG if you have certain side effects.
- Take WELIREG with or without food.

- Swallow WELIREG tablets whole. **Do not** chew, crush, or split WELIREG tablets.
- If you miss a dose of WELIREG, take it as soon as possible on the same day. Then take your next dose of WELIREG at your regular time the next day. **Do not** take extra tablets to make up for the missed dose.
- If you vomit after taking a dose of WELIREG, **do not** take an extra dose. Take your next dose at your regular time the next day.
- If you take too much WELIREG, call your healthcare provider or go to the nearest emergency room right away.

What are the possible side effects of WELIREG?

WELIREG may cause serious side effects, including:

- See “**What is the most important information I should know about WELIREG?**”

The most common side effects of WELIREG include:

- feeling tired
- increased creatinine (kidney function test)
- headache
- feeling dizzy
- increased blood sugar (glucose) levels
- nausea

WELIREG may cause fertility problems in males and females, which may affect your ability to have children. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of WELIREG.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store WELIREG?

- Store WELIREG at room temperature between 68°F to 77°F (20°C to 25°C).
- The WELIREG bottle contains 2 desiccant canisters that help keep your medicine dry. **Do not** eat the desiccant canisters.

Keep WELIREG and all medicines out of the reach of children.

General information about the safe and effective use of WELIREG.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use WELIREG for a condition for which it was not prescribed. Do not give WELIREG to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about WELIREG that is written for health professionals.

What are the ingredients in WELIREG?

Active ingredient: belzutifan

Inactive ingredients: croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, and silicon dioxide. The film-coating contains FD&C Blue #2 aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Issued: 08/2021

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Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Do not use if inner seal is broken or missing.

Recommended Dosage: See Prescribing Information.

NDC 0006-5331-01

WeliregTM
(belzutifan) tablets

40 mg

Dispense the accompanying Medication Guide to each patient.
Each tablet contains 40 mg of belzutifan.

Rx only

90 Tablets



Mundipharma Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO. INC., Whitehouse Station, NJ 08889, USA
Manufactured by: MSD International GmbH
Welireg (belzutifan) tablets (40 mg tablets)
Belzutifan (active ingredient) made in China.
Formulated in Ireland.

MERCK

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