TREATMENT GUIDE

MANAGING PATIENTS WHO HAVE BEEN PRESCRIBED **WELIREG**

WELIREG 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.

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).

IN THIS GUIDE:

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.**

WELIREG can cause severe anemia that can require blood transfusion. Monitor for anemia before initiation of, and periodically throughout, treatment.

WELIREG can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalization. Monitor oxygen saturation before initiation of, and periodically throughout, treatment.

Before prescribing WELIREG, please read the additional Selected Safety Information on pages 8–10 and the accompanying Prescribing Information, including the Boxed Warning about embryo-fetal toxicity. The Medication Guide also is available.

WELIREG™ (belzutifan) 40 mg tablets

Once-daily oral dosing

The recommended dose of WELIREG is 120 mg (three 40-mg tablets) once daily until disease progression or unacceptable toxicity

Not actual size.

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.

LITESPARK-004 STUDY DESIGN: Patients (N=61) had VHL-associated RCC diagnosed based on a VHL germline alteration and with at least 1 measurable solid tumor (as defined by RECIST v1.1) localized to the kidney. 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 1 measurable solid tumor in brain/spine or pancreas, respectively, as defined by RECIST v1.1 and identified by central independent review committee (IRC). The study excluded patients with metastatic disease. Patients received WELIREG 120 mg once daily until progression of disease or unacceptable toxicity. Median age of patients was 41 years (range: 19 to 66 years). Of the 61 patients included in the study, 3.3% were age 65 years or older, and 53% were male. Ninety percent were White, 3.3% were Black or African-American, 1.6% were Asian, and 1.6% were Native Hawaiian or other Pacific Islander. Eighty-two percent had an Eastern Cooperative Oncology Group performance status (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 IRC was 2.2 cm (range 1.0 to 6.1 cm). Median time from initial radiographic diagnosis of VHL-associated RCC tumors that led to enrollment to the time of treatment with WELIREG was 17.9 months (range: 2.8 to 96.7 months). Seventy-seven percent of patients had prior surgical procedures for RCC. The major efficacy end point for the treatment of VHL-associated RCC was objective response rate (ORR) measured by radiology assessment using RECIST v1.1 as assessed by IRC. Additional efficacy end points included duration of response (DOR) and time to response (TTR).

LITESPARK-005 STUDY DESIGN: Patients (N=746) had unresectable, locally advanced or metastatic clear cell RCC and progression following PD-1/L1 checkpoint inhibitor and VEGF-TKI therapies (in sequence or in combination), with a maximum of 3 prior treatment lines. Patients were randomized 1:1 and received WELIREG 120 mg once daily (n=374) or everolimus 10 mg once daily (n=372) until progression of disease or unacceptable toxicity. 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 outcomes were OS and PFS, measured by radiology assessment using RECIST v1.1. Additional efficacy outcomes included ORR and DOR.

RECIST v1.1 = Response Evaluation Criteria In Solid Tumors v1.1.

Recommended dose modifications for adverse events

Adverse reaction	Severity[a]	Dose modification
ANEMIA	Hemoglobin <8 g/dL or transfusion indicated	• Withhold until hemoglobin ≥8 g/dL • Resume at the same or reduced dose; or discontinue depending on the severity of anemia
	Life-threatening or urgent intervention indicated	• Withhold until hemoglobin ≥8 g/dL • Resume at reduced dose or permanently discontinue
HYPOXIA	Decreased oxygen saturation with exercise (eg, 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 (eg, pulse oximeter <88% or PaO_2 ≤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	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

[a]Graded per NCI CTCAE v4.0.

Dose reductions (if appropriate)

FIRST DOSE REDUCTION **80 mg orally once daily**

SECOND DOSE REDUCTION **40 mg orally once daily**

THIRD DOSE REDUCTION **Permanently discontinue**

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LITESPARK-004

An open-label clinical trial for patients (n=61) with VHL disease–associated RCC, CNS hemangioblastomas, or pNET, not requiring immediate surgery

LITESPARK-004 adverse reaction profile

Adverse reactions occurring in ≥10% of patients treated with WELIREG

	WELIREG (N=61)	
Adverse Reaction	**All Grades[a] (%)**	**Grade 3–4 (%)**
General		
Fatigue[b]	64	5
Nervous System		
Headache[b]	39	0
Dizziness[b]	38	0
Gastrointestinal		
Nausea	31	0
Constipation	13	0
Abdominal pain[b]	13	0
Eye Disorders		
Visual impairment[c]	21	3.3
Infections		
Upper respiratory tract infection[b]	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

[a]Graded per NCI CTCAE v4.0.
[b]Includes other related terms.
[c]Includes visual impairment, vision blurred, central retinal vein occlusion, and retinal detachment.

The median duration of exposure to WELIREG was 68 weeks (range: 8.4 to 104.7 weeks).

Patients on WELIREG experienced a low rate of permanent discontinuation (3.3%) due to ARs. ARs that resulted in permanent discontinuation of WELIREG were dizziness and opioid overdose (1.6% each).

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).

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; AR = adverse reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

LITESPARK-004

An open-label clinical trial for patients (n=61) with VHL disease–associated RCC, CNS hemangioblastomas, or pNET, not requiring immediate surgery

LITESPARK-004 select laboratory abnormalities

Select laboratory abnormalities (≥10%) that worsened from baseline in patients who received WELIREG in LITESPARK-004

	WELIREG (N=61)	
Laboratory Abnormality[d]	**All Grades** (%)	**Grade 3–4** (%)
Hematology		
Decreased hemoglobin	93	7
Decreased leukocytes	11	0
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

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

Monitor for anemia and oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG.

In the LITESPARK-004 clinical trial:

- Decreased hemoglobin occurred in 93% of patients and 7% had Grade 3 events
  - Median time to onset of anemia was 31 days (range: 1 day to 8.4 months)
- Hypoxia occurred in 1.6% of patients

In LITESPARK-004, patients received WELIREG for a median duration of 68 weeks

(range: 8.4 to 104.7 weeks)

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WELIREG™ (belzutifan) 40 mg tablets

LITESPARK-005

An open-label clinical trial for patients (n=746) with advanced RCC following treatment with both anti–PD-1/L1 and VEGF-TKI therapies

LITESPARK-005 adverse reaction profile

Adverse reactions (≥10%) in patients with advanced RCC receiving WELIREG (belzutifan) in LITESPARK-005

Adverse Reaction	WELIREG (n=372)		Everolimus (n=360)	
	All Grades[a] (%)	Grade 3–4 (%)	All Grades[a] (%)	Grade 3–4 (%)
General				
Fatigue[b]	43	3.2	41	6
Edema[b]	20	0.5	23	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[b]	34	1.1	27	2.2
Gastrointestinal				
Nausea	17	0.5	11	0.3
Constipation	15	0	8	0
Vomiting	11	0.8	8	0.8
Diarrhea[b]	11	1.3	19	1.4
Abdominal pain[b]	10	0.8	8	0.3
Respiratory, Thoracic, and Mediastinal				
Dyspnea[b]	16	1.6	16	2.5
Hypoxia	15	10	1.4	1.4
Metabolism and Nutrition				
Decreased appetite	13	1.1	16	0
Nervous Systems				
Headache[b]	12	0.5	8	0.3
Dizziness[b]	11	0	1.9	0

[a]Graded per NCI CTCAE v5.0.
[b]Includes other related terms.

The median duration of exposure for WELIREG was 7.6 months (range: 0.1–28.5 months).

Serious ARs occurred in 38% of patients who received WELIREG.

Permanent discontinuation of WELIREG due to ARs occurred in 6% of patients. ARs which resulted in permanent discontinuation (≥0.5%) of WELIREG were hypoxia (1.1%), anemia (0.5%), and hemorrhage (0.5%).

Dosage interruptions of WELIREG due to an AR occurred in 39% of patients.

Dose reductions of WELIREG due to an AR occurred in 13% of patients.

LITESPARK-005

An open-label clinical trial for patients (n=746) with advanced RCC following treatment with both anti–PD-1/L1 and VEGF-TKI therapies

LITESPARK-005 select laboratory abnormalities

Select laboratory abnormalities (≥20%) that worsened from baseline in patients with advanced RCC who received WELIREG in LITESPARK-005

Laboratory Test[a]	WELIREG		Everolimus	
	All Grades[b] (%)	Grade 3–4 (%)	All Grades[b] (%)	Grade 3–4 (%)
Hematology				
Decreased hemoglobin	88	29	76	17
Decreased lymphocytes	34	8	53	20
Chemistry				
Increased creatinine	34	4.7	43	5.1
Increased alanine aminotransferase	32	2.2	40	1.1
Decreased sodium	31	1.6	36	0.8
Increased potassium	29	2.5	20	2.8
Increased aspartate aminotransferase	27	2.2	38	2
Decreased glucose	22	1.1	19	1.1
Decreased calcium	21	1.1	45	3.1

[a]Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: WELIREG (range: 359 to 366 patients) and everolimus (range: 351 to 356 patients).
[b]Graded per NCI CTCAE v5.0.

Monitor for anemia and oxygen saturation before initiation of, and periodically throughout, treatment with WELIREG.

In the LITESPARK-005 clinical trial:

- Decreased hemoglobin occurred in 88% of patients and 29% had Grade 3 events
  - Median time to onset of anemia was 29 days (range: 1 day to 16.6 months)
- Hypoxia occurred in 15% of patients and 10% had Grade 3
  - Median time to onset of hypoxia was 30.5 days (range: 1 day to 21.1 months)

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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.
- 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 safety of erythropoiesis-stimulating agents (ESAs) for treatment of anemia in patients with VHL disease treated with WELIREG has not been established.
- 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 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-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.

SELECTED SAFETY INFORMATION *(continued)*

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%), 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%).

Selected Safety Information continues on the following page →

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WELIREG™ (belzutifan) 40 mg tablets

SELECTED SAFETY INFORMATION *(continued)*

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.

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NOTES

WELIREG™
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LEARN MORE ABOUT WELIREG

for treating patients with advanced RCC or certain VHL disease–associated tumors

SCAN HERE FOR MORE INFORMATION

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WELIREG™ (belzutifan) 40 mg tablets