Prescribing Information

merck.com/product/usa/pi_circulars/w/welireg/welireg_pi.pdf

Medication Guide

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WELIREG™ (belzutifan) 40 mg tablets

A Reference Guide to Discussing WELIREG With Patients With Eligible VHL Disease-Associated Tumors

Considerations for Discussions With Your Patients Who May Be Prescribed WELIREG

INDICATION

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.

Overview of the Reference Guide

- This guide was developed for health care providers treating patients with VHL disease-associated tumors who are eligible for **WELIREG**. Its purpose is to help you facilitate conversations with such patients before and during treatment with **WELIREG**, given that VHL disease is rare and may be present in a very small proportion of your patients.
- The guide includes suggested topics, patient-friendly language, and data that may be helpful to discuss with your eligible patients.
- **This guide is not intended to replace the full Prescribing Information or Selected Safety Information for WELIREG.**

Hypothetical Patient Profile: Meet Mia

34 years old with family history and confirmed VHL disease diagnosis

- Mia's father has VHL disease and recently underwent a partial nephrectomy.
- She is currently asymptomatic but presented with **VHL disease-associated RCC and CNS hemangioblastoma**.
- Mia's neuro-oncologist **discussed her case with a multidisciplinary care team**. Given the size of Mia's tumors and her asymptomatic presentation, **she did not require immediate surgery**.

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 throughout and on pages 4-5 and the accompanying Prescribing Information, including the Boxed Warning about embryo-fetal toxicity. The Medication Guide also is available.

Topics and Questions to Consider With Your Eligible Patients

VHL Disease Education

- Once their diagnosis is confirmed, it is important for patients to understand VHL disease and its management. Since there is no cure for VHL disease, continual management and monitoring are needed.
- Patients with rare diseases such as VHL disease are generally knowledgeable about their condition and treatments, but they may need additional resources. Consider connecting your patients with patient advocacy groups or providing educational resources on VHL disease and treatment options.
- Because VHL disease is a lifelong syndrome, consider discussing treatment goals with patients and regularly revisit the conversation, especially for a patient like Mia, who does not require immediate surgery.
- Identify affected organs and manifestations to determine patients' eligibility for **WELIREG**.

Consider describing VHL disease using the following language with your patients

"VHL disease is a rare, genetic, lifelong syndrome that can cause recurrent tumor development in the kidneys, brain, spinal cord, and pancreas.[1-3]"

What Is WELIREG™ (belzutifan)?

- You may want to discuss the mechanism of action of **WELIREG** in simple terms and discuss how **WELIREG** is a systemic therapy that is orally administered.
- Your patients may want to know that **WELIREG** is the only approved systemic therapy for patients with certain VHL disease-associated tumors, not requiring immediate surgery. Discussions with multiple specialists may be needed to determine if **WELIREG** is right for the patient.

Consider describing the mechanism of action of WELIREG to your patients using the following language

"Cells in the body contain a protein called VHL. When the VHL protein is working normally, and when the cell is getting enough oxygen, VHL protein helps to break down another protein called HIF-2α, and contributes to maintaining normal cell function. In patients with VHL disease, VHL protein works improperly. When this happens, or when the cell is not getting enough oxygen, too much HIF-2α can build up. HIF-2α then moves to the nucleus and joins another protein called HIF-1β. This turns on genes that can contribute to tumor growth in VHL disease. **WELIREG** attaches to HIF-2α to prevent it from joining HIF-1β in the nucleus."

Consider using the language below when describing WELIREG

"**WELIREG** is a prescription medicine used to treat adults with VHL disease who need treatment for a type of kidney cancer called RCC, tumors in the brain and spinal cord called CNS hemangioblastomas, or a type of pancreatic cancer called pNET, that do not need surgery right away. It is taken by mouth at the same time each day."

Mia | 34 years old
Hypothetical Patient

- Has family history and confirmed VHL disease diagnosis
- Asymptomatic VHL disease-associated RCC and CNS hemangioblastoma
- Given Mia's asymptomatic presentation, **she did not require immediate surgery**. Therefore, the care team decided to recommend **WELIREG**.
- Mia wanted to start treatment as soon as possible to potentially reduce her risk of disease progression.

Consider asking

- "Do you have any questions about the importance of continued management for your VHL disease?"
- "What are your treatment goals?"

Patients can use the Welcome to WELIREG booklet or set reminders to help them remember to take WELIREG at the same time every day.

Scan for the Welcome to WELIREG booklet

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Before Starting

Topics and Questions to Consider With Your Eligible Patients

Adverse Reactions for WELIREG: Potential Embryo-Fetal Toxicity

- **WELIREG** carries a black boxed warning regarding potential embryo-fetal toxicity that should be discussed with all patients of reproductive potential.
- It is important to advise patients to use an effective form of nonhormonal birth control and that birth control methods that contain hormones may not work as well during treatment with **WELIREG**.

Consider the important information below regarding potential embryo-fetal toxicity in discussions

- Advise pregnant women and females of reproductive potential of the risk to a fetus. Advise females to inform their health care provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective nonhormonal contraception during treatment with **WELIREG** and for 1 week after the last dose.
- 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.

How to Take WELIREG

- It is important to ensure that your patients understand how to appropriately take **WELIREG**, a systemic treatment that is taken by mouth daily.
- Advise patients to take **WELIREG** exactly as prescribed and continue taking it without stopping or modifying the dosage without contacting their care team. Remind patients to inform the care team if they encounter any difficulties with filling their **WELIREG** prescription.
- Tell patients to inform the care team right away if they experience any signs or symptoms of side effects.
- Inform patients that the dosage may be adjusted or they may be instructed to temporarily or permanently stop treatment with **WELIREG** if they experience certain side effects.

Key dosing information for WELIREG

- 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 every 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.

Not actual size.

120 mg (three 40-mg tablets) → 24 HOURS → Orally, once daily → With or without food

Mia | 34 years old
Hypothetical Patient

- Mia mentioned that she and her partner are considering having children in the future and asked whether **WELIREG** could affect their family planning.

Consider asking

- "Are you and your partner having any family planning discussions?"

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

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.

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%).

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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.

Scan to Access a Treatment Guide for Managing Adverse Reactions

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Topics and Questions to Consider With Your Eligible Patients

LITESPARK-004 Efficacy

- Your patients may have questions on how well **WELIREG™ (belzutifan)** works to treat VHL disease-related RCC, CNS hemangioblastoma, and pNET before starting treatment.
- It is important to set appropriate expectations on the efficacy and duration of the treatment. It may take several months of treatment to see changes to a tumor, if any.

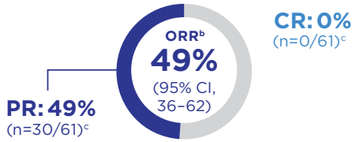
Key information on the LITESPARK-004 study design

LITESPARK-004 was an open-label clinical trial of **WELIREG** in patients with VHL disease-associated RCC. Patients had ≥1 measurable solid tumor localized to the kidney, as defined by RECIST v1.1. Some patients also had other VHL disease-associated tumors, CNS hemangioblastomas and pNET, based on the presence of ≥1 measurable solid tumor in the brain, spine, or pancreas. Patients with metastatic disease were excluded. Patients received **WELIREG** 120 mg PO daily until disease progression or unacceptable toxicity. The major efficacy endpoint for VHL disease-associated RCC was ORR by radiology assessment. Additional efficacy end points were DOR and TTR.

Key efficacy data from LITESPARK-004

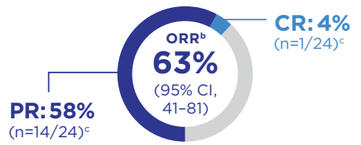
Patient Subgroups

RCC (n=30/61)[a]



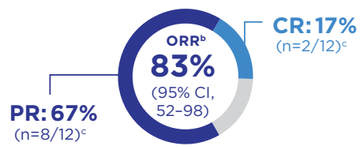
- **Median DOR:** Not reached[d] (range: 2.8+ to 22+ months)
- **56%** of patients who responded (n=17/30) **maintained a response that lasted ≥12 months**

CNS (n=15/24)[e]



- **Median DOR:** Not reached[d] (range: 3.7+ to 22+ months)
- **73%** of patients who responded (n=11/15) **maintained a response that lasted ≥12 months**

pNET (n=10/12)[e]



- **Median DOR:** Not reached[d] (range: 11+ to 19+ months)
- **50%** of patients who responded (n=5/10) **maintained a response that lasted ≥12 months**

[a]All patients with a response were followed for a minimum of 18 months from the start of treatment. [b]Measured by radiology assessment by IRC using RECIST v1.1. [c]Complete response defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm. Partial response defined as ≥30% decrease in the sum of the longest diameters of target lesions compared with baseline.[4] [d]Median DOR could not be estimated by Kaplan-Meier method since the majority of patients who responded to treatment maintained their response (did not experience disease progression per RECIST v1.1) at the time of data cutoff.[5] [e]Number of patients with measurable solid lesions, based on IRC assessment. +Denotes ongoing response.

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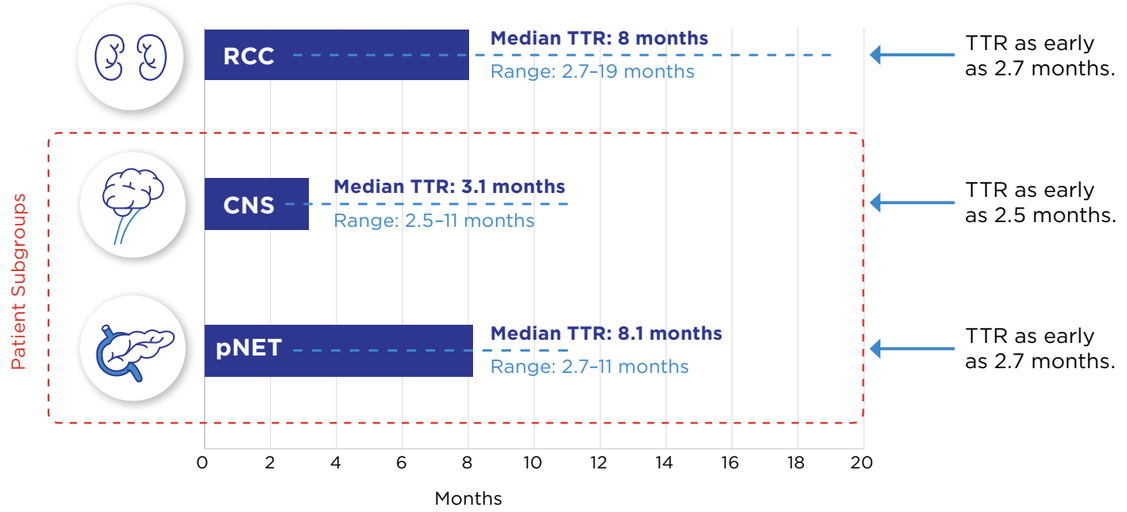
Before Starting

Topics and Questions to Consider With Your Eligible Patients

Time to Response (TTR) from LITESPARK-004



Communicating LITESPARK-004 Efficacy

You may want to discuss the efficacy data from the LITESPARK-004 trial in simple language that patients can understand to help them make informed decisions.

Mia | 34 years old
Hypothetical Patient

- During research about **WELIREG**, Mia had trouble understanding some of the information about the clinical trial and asked her neuro-oncologist to explain the trial and the data.

Consider describing the LITESPARK-004 end points to your patients using the following language

- **ORR:** "Percentage of patients whose tumors completely or partially shrank after starting therapy."
- **DOR:** "How long patients who responded to treatment continued to respond."
- **TTR:** "Among patients who responded, the time it took them to respond after starting treatment."

Consider describing the LITESPARK-004 efficacy data to your patients using the following language

- "**WELIREG** helped certain VHL disease-related tumors shrink."
- **RCC:** "49% of patients (30 out of 61) had tumors in their kidneys partially shrink."
- **CNS:** "63% of patients (15 out of 24) had tumors in their brain and spinal cord partially or completely shrink. 14 out of these 24 patients had their tumors partially shrink and 1 saw their tumors completely shrink."
- **pNET:** "83% of patients (10 out of 12) saw tumors in their pancreas partially or completely shrink. 8 out of these 12 patients had their tumors partially shrink and 2 had their tumors completely shrink."

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Before Starting

Topics and Questions to Consider With Your Eligible Patients

Adverse Reactions Associated With WELIREG™ (belzutifan)

- Before starting, potential adverse reactions associated with **WELIREG** should be discussed with your patients. Younger patients, in particular, may be more concerned about how potential adverse reactions might affect their lives.
- After starting **WELIREG**, your patients may experience side effects. Make sure your patients know the importance of notifying the care team of any side effects, and that you may change their dose, temporarily stop, or permanently stop treatment with **WELIREG** if they have certain side effects. Depending on the types or severity of any side effects, **WELIREG** may be withheld, reduced, or discontinued.
- Two important potential adverse reactions with **WELIREG** are **anemia** and **hypoxia**. Your patients may be unfamiliar with these conditions, so it is important to explain the symptoms, potential risks, and when to seek medical care.
- Ensure that your patients know how to contact their care team in case they experience side effects.

Mia | 34 years old
Hypothetical Patient

- Mia had concerns about potential adverse reactions associated with **WELIREG** and asked her neuro-oncologist what she should expect.

Consider reviewing the most common adverse reactions and laboratory abnormalities from LITESPARK-004 before starting treatment to set appropriate expectations with your patients.

Most Common (≥25%) Adverse Reactions and Laboratory Abnormalities in Adults With VHL Disease

- Decreased hemoglobin
- Increased creatinine
- Increased glucose
- Dizziness
- Fatigue
- Headache
- Nausea

Consider the following key information in discussions about anemia and hypoxia with your patients

- 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 health care provider if they experience any symptoms suggestive of anemia, including fatigue, feeling cold, dyspnea, angina, and tachycardia.
- 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 health care provider if they experience any symptoms suggestive of hypoxia, including dyspnea and tachycardia.

Consider using the following language when discussing some of the most common adverse reactions with WELIREG

- **Fatigue:** “Tiredness”
- **Decreased hemoglobin:** “Lower levels of a protein within red blood cells that carries oxygen from the lungs to the tissues and organs”
- **Increased glucose:** “Increased blood sugar levels”
- **Increased creatinine:** “Higher levels of a waste protein used to measure kidney function”

Consider using the following language when discussing anemia and hypoxia with your patients

- **Anemia:** “Low red blood cell counts”
  - Symptoms that may suggest anemia: “Tiredness, feeling cold, shortness of breath, chest pain, and fast heartbeat”
- **Hypoxia:** “Low oxygen levels in your body”
  - Symptoms that may suggest hypoxia: “Shortness of breath and fast heartbeat”

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After Starting

Topics and Questions to Consider With Your Eligible Patients

Managing Adverse Reactions Associated With WELIREG

- It is important to monitor for anemia and check oxygen saturation before initiation of, and periodically throughout, treatment with **WELIREG**. Transfuse patients as clinically indicated.
- The dosage modifications below may be used to manage adverse reactions associated with **WELIREG**.

Mia | 34 years old
Hypothetical Patient

- Mia called her neuro-oncologist’s office and reported experiencing tiredness, weakness, and shortness of breath.
- At the appointment, Mia had a hemoglobin level of 7.5 g/dL, and she was diagnosed with Grade 3 anemia.

Consider the following recommended dosage modifications to manage adverse reactions

Recommended Dosage Modifications for Anemia

Hb <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 a reduced dose or permanently discontinue.

Recommended Dosage Modifications for 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.

Recommended Dosage Modifications for 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.

Dose Reductions

First reduction:
80 mg orally once daily

Second reduction:
40 mg orally once daily

Third reduction:
Permanently discontinue **WELIREG**

Consider asking

- “Have your treatment goals changed?”
- “Has anything else changed since you started taking **WELIREG?**”
- “Have you been experiencing any signs or symptoms of side effects?”
- “Have you been feeling tired, cold, or short of breath?”

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Talk to your appropriate patients with eligible VHL disease-associated tumors to help them know what to expect during systemic treatment with **WELIREG.**

For resources to help patients get access and support for **WELIREG**, visit The Merck Access Program website.

Scan to Learn More About What to Expect When Prescribing WELIREG

SELECTED SAFETY INFORMATION

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Abbreviations: CI = confidence interval; CR = complete response; DOR = duration of response; Hb = hemoglobin; HIF-1β = hypoxia-inducible factor 1 beta; HIF-2α = hypoxia-inducible factor 2 alpha; IRC = independent review committee; ORR = objective response rate; PaO_2 = partial pressure of oxygen; PO = by mouth; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors v1.1; TTR = time to response.

References: 1. Varshney N et al. *J Kidney Cancer VHL.* 2017;4(3):20–29. **2.** Ashouri K et al. *J Kidney Cancer VHL.* 2015;2(4):163–173. **3.** Von Hippel-Lindau Disease. National Organization for Rare Disorders. Last updated October 25, 2023. Accessed November 13, 2023. rarediseases.org/rare-diseases/von-hippel-lindau-disease/?filter=ovr-ds-resources#completereport **4.** Eisenhauer EA et al. *Eur J Cancer.* 2009;45(2):228–247. **5.** Delgado A, Guddati AK. *Am J Cancer Res.* 2021;11(4):1121–1131.

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