Drug Monograph

A - Drug Name

belzutifan

COMMON TRADE NAME(S): Welireg®

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B - Mechanism of Action and Pharmacokinetics

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α), a transcription factor that promotes cell adaptation to hypoxia. Impairment of the von Hippel-Lindau (VHL) protein function prevents HIF-2α degradation, leading to accumulation of HIF-2α. Inhibition of HIF-2α results in reduced expression of downstream genes involved in cellular proliferation, angiogenesis, and tumor growth.

Absorption	Effects with food	No significant effect on drug exposure when given with a high-fat, high-calorie meal, although a delayed Tmax was observed.
	Time to reach steady state	3 days
Distribution	PPB	45%
Metabolism	Belzutifan is primarily metabolized by UGT2B17 and CYP2C19.	
	Active metabolites	Unknown
	Inactive metabolites	Yes
Elimination	Half-life	14 hours

Feces	51.7%, mostly as inactive metabolites
Urine	49.6% (6% unchanged)

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C - Indications and Status

Health Canada Approvals:

- Von Hippel-Lindau (VHL) disease
- Renal Cell Carcinoma (RCC)

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low – No routine prophylaxis; PRN recommended

The following table lists adverse effects that occurred in ≥ 5% of patients with advanced RCC treated with belzutifan versus everolimus in a randomized Phase 3 study. This table also includes severe or life-threatening adverse effects from other studies.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Hypertension (6%)	E
	Thromboembolism (3%)	E
Dermatological	Rash (8%)	E
Gastrointestinal	Abdominal pain (11%)	E
	Anorexia (15%)	E
	Constipation (17%)	E
	Diarrhea (12%)	E
	Nausea, vomiting (18%)	E
	Weight gain (6%)	E

General	Edema (20%)	E
	Fatigue (46%) (3% severe)	E
Hematological	Anemia (83%) (33% severe)	E D
	Hemorrhage (10%) (3% severe, including CNS)	E
Hepatobiliary	↑ LFTs (12%)	E
Metabolic / Endocrine	Hyperglycemia (3%)	E
Musculoskeletal	Musculoskeletal pain (38%)	E
Nervous System	Dizziness (14%)	E
	Headache (12%)	E
Ophthalmic	Visual disorders (8%) (may be severe, including retinal vein occlusion, retinal detachment)	E
Renal	Creatinine increased (9%)	E
Respiratory	Cough, dyspnea (17%)	E
	Hypoxia (15%) (11% severe)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for belzutifan include anemia, fatigue, musculoskeletal pain, edema, nausea, vomiting, constipation, cough, dyspnea, anorexia, hypoxia, and dizziness.

Severe **anemia** may require blood transfusion and erythropoiesis stimulating agents (ESAs). The safety of ESAs in patients with VHL disease treated with belzutifan has not been established. Of the renal cell cancer patients with anemia, 22% received transfusions only, 20% received ESAs only and 14% received both transfusion and ESAs. Baseline hemoglobin (≤ 120g/L) may increase the risk of developing ≥ Grade 3 anemia. Median time to onset of all Grade anemia events was ~1 month in clinical trials.

Hypoxia may be asymptomatic. Healthcare providers may instruct patients to monitor oxygen saturation at home at their discretion. Severe hypoxia may require discontinuation, supplemental oxygen, or hospitalization. Of the patients with hypoxia, 70% were treated with oxygen therapy. The median onset of hypoxia was reported to be 1 month in clinical trials.

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E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Adults:

Oral: 120 mg Daily

Dosage with Toxicity:

Dose Level	Belzutifan (mg daily)
0	120
-1	80
-2	40
-3	Discontinue

Toxicity	Severity/Grade	Action
Anemia	Grade 3 or transfusion indicated	Hold* Resume at same dose or at 1 dose level ↓ OR consider discontinuing depending on severity and/or persistence of toxicity.
	Grade 4	Hold* Resume at 1 dose level ↓ OR discontinue. Discontinue if recurrence of Grade 4.
Hypoxia	Grade 2	Consider continuing or holding until resolved. If held, consider resuming at reduced dose depending on severity and/or persistence of toxicity.
	Grade 3	Hold until resolved. Resume at 1 dose level ↓ OR discontinue depending on severity and/or persistence of toxicity.
	Grade 4 or recurrent symptomatic hypoxia	Discontinue.
Other Adverse Reactions	Grade 3	Hold* Consider resuming at 1 dose level ↓. Discontinue if recurrence of Grade 3.
	Grade 4	Discontinue.

*Do not restart until toxicity resolved to ≤ Grade 2.

Dosage with Hepatic Impairment:

Bilirubin		AST	Belzutifan Dose
≤ ULN	and	> ULN	No dose adjustment recommended
>1 to 1.5 x ULN	and	Any	
> 1.5 x ULN	and	Any	No data

Dosage with Renal Impairment:

Creatinine Clearance*	Belzutifan Dose
≥ 30	No dose adjustment recommended
< 30	No data

*Reported as eGFR in mL/min/1.73m^2

Dosage in the elderly:

No dose adjustment is needed in patients ≥ 65 years of age. No overall difference in safety or efficacy was reported between patients ≥ 65 years of age and over and younger patients. Differences in belzutifan tolerability profile were observed in patients ≥ 65 years of age compared to younger patients.

Dosage based on gender:

No dose adjustment required. Population pharmacokinetics analysis showed a 1.6-fold higher belzutifan exposure in female patients compared to male patients.

Dosage based on ethnicity:

No dose adjustment required. Population pharmacokinetics analysis showed a 2.3-fold higher belzutifan exposure in Asian patients compared to Caucasian patients. This difference can be due to higher frequencies of UGT2B17 poor metabolizers and combined UGT2B17 and CYP2C19 poor metabolizers in Asian patients, compared to Caucasian and African American patients (also refer to Drug Interactions section).

Children:

The safety and efficacy of belzutifan in pediatric patients under 18 years of age have not been established.

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F - Administration Guidelines

- Administer belzutifan with or without food.
- Tablets should be swallowed whole. Do not chew, crush, or split the tablets.
- If a dose is missed, it can be given as soon as possible on the same day. Then administer the scheduled dose on the next day. Do not give extra tablets to make up for the missed dose.
- If a patient vomits after taking belzutifan, do not give another dose. The next dose should be given at the scheduled time on the following day.
- Store at room temperature (15°C to 30°C).

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Caution with driving or using machinery as dizziness may occur with treatment.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: No
- Mutagenicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Pregnancy:
  Belzutifan is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **1 week** after the last dose.
  Use non-hormonal (e.g., barrier) methods of contraception since belzutifan may reduce the effectiveness of hormonal contraceptives (See Interactions section).
- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **1 week** after the last dose.
- Fertility effects: Probable
  Documented in animal studies. Discuss fertility preservation with patients prior to starting treatment.

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H - Interactions

Belzutifan is primarily metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4.

Belzutifan is a moderate CYP3A4 inducer.

Belzutifan is a weak P-gp, OATP1B1 and OATP1B3 substrate, and inhibits MATE2K; the clinical significance is unknown.

Individuals who are UGT2B17 poor metabolizers or combined UGT2B17 and CYP2C19 poor metabolizers have higher belzutifan exposures (2.7-fold or 3.3 -fold respectively). No dose adjustment is recommended. Monitor closely for adverse reactions.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Sensitive CYP3A4 substrates (i.e. midazolam)	↓ CYP3A4 substrates concentration and/or efficacy. (May be more pronounced in patients who are combined UGT2B17 and CYP2C19 poor metabolizers.)	Belzutifan is a moderate CYP 3A4 inducer	Avoid concomitant use with CYP3A4 sensitive substrates for which minimal concentration ↓ may lead to substrates' therapeutic failures. If must co-administer, ↑ dosage of CYP3A4 substrate as per substrate's product monograph.
Hormonal contraceptives	Coadministration may lead to contraceptive failure or an increase in breakthrough bleeding	Belzutifan is a moderate CYP 3A4 inducer	Avoid concomitant use with hormonal contraceptives. Advise patients of the need for highly effective non-hormonal contraception methods.
UGT2B17 or CYP2C19 inhibitors	↑ belzutifan exposure and/or toxicity	Belzutifan is metabolized by UGT2B17 and CYP2C19	Caution; monitor for increased adverse reactions.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, at each visit, and as clinically indicated
Oxygen saturation	Baseline and at each visit, and as clinically indicated (May consider monitoring at home when starting treatment and as clinically indicated)
Liver function tests	Baseline, at each visit, and as clinically indicated
Renal function tests	Baseline, at each visit, and as clinically indicated
Clinical toxicity assessment for fatigue, musculoskeletal pain, edema, ophthalmic or GI effects, dyspnea, bleeding	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- Belzutifan – For the treatment of adult patients with von Hippel-Lindau (VHL) disease, based on criteria

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K - References

Belzutifan [Drug information]. UpToDate Inc. (2025). Accessed January 21, 2025.

Choueiri TK, Powles T, Peltola K, et al Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma. N Engl J Med. 2024 Aug 22;391(8):710-721. doi: 10.1056/NEJMoa2313906.

Jonasch E, Donskov F, Iliopoulos O, et al. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med. 2021 Nov 25;385(22):2036-2046. doi: 10.1056/NEJMoa2103425.

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Product Monograph: WELIREG® (belzutifan). Merck Canada Inc. December 17, 2024.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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