DRUG NAME: Belzutifan

SYNONYM(S): MK6482[1], PT2977[1]

COMMON TRADE NAME(S): WELIREG®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Belzutifan is an orally administered small molecule inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is a transcription factor that has a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2α is targeted for degradation by the von Hippel-Lindau (VHL) protein. In VHL disease, the lack of functional VHL proteins causes an accumulation of HIF-2α, which subsequently interacts with hypoxia-inducible factor 1 beta (HIF-2β) and forms a transcriptional complex that induces expression of downstream genes. Belzutifan binds to HIF-2α and prevents it from forming this complex, resulting in reduced transcription and expression of HIF-2α target genes, including genes associated with cellular proliferation, angiogenesis, and tumour growth.[1-4]

PHARMACOKINETICS:

Oral Absorption	T_{max} = 1-2 hours; steady state after 3 days	
Distribution	blood to plasma concentration ratio = 0.88	
	cross blood brain barrier?	no information found
	volume of distribution	119-130 L
	plasma protein binding	45%
Metabolism	primarily metabolized by UGT 2B17 and CYP 2C19 and to a lesser extent by CYP 3A4; poor metabolizers of both UGT 2B17 and CYP 2C19 are projected to have up to 2.3-fold higher belzutifan exposures	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	equally excreted in urine and feces	
	urine	49.6% (primarily as inactive metabolites)
	feces	51.7% (primarily as inactive metabolites)
	terminal half life	14 h
	clearance	6-7.3 L/h
Sex	no clinically significant difference	
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[1,3,5] unless specified otherwise.

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USES:

Primary uses:

*Renal cell cancer

*Pancreatic neuroendocrine tumour

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- patients with ***baseline hemoglobin ≤120 g/L*** may be at increased risk of developing grade ≥3 anemia; monitor for anemia prior to initiating treatment[3]
- ***hypoxia*** may occur; monitor oxygen saturation with pulse oximetry prior to starting treatment[3,5]
- belzutifan may affect ***wound healing*** due to its effect on angiogenesis/cellular proliferation; suggest holding belzutifan starting 5-7 days prior to surgery and not resuming post-surgery until adequate wound healing has been achieved[6]

Special populations: Patients who are ***dual UGT2B17 and CYP2C19 poor metabolizers*** may have higher belzutifan exposures and increased incidence and/or severity of adverse reactions.[3,5]

Carcinogenicity: Carcinogenicity studies have not been conducted. Secondary malignancies have been reported in clinical trials with belzutifan; clinical significance is unknown.[3]

Mutagenicity: Not mutagenic in Ames test. Belzutifan was not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[3,5]

Fertility: In animal studies, degeneration/atrophy of the testes and hypospermia/cellular debris of the epididymis were observed at exposures 0.1-0.2 times those seen following human clinical exposure. Some findings were not reversible at the end of the recovery period and were associated with decreased sperm count, motility, and abnormal sperm morphology.[3,5]

Pregnancy: In animal studies, embryo-fetal lethality (post-implantation loss), reduced fetal body weights, fetal rib malformations, and reduced skeletal ossification were observed at exposures 0.2-1 times those seen following human clinical exposure. Pregnancy tests are recommended for female patients of childbearing potential prior to starting treatment. For female patients of childbearing potential and male patients with female partners of childbearing potential, contraception is recommended during treatment and for at least 1 week after the last dose. Belzutifan may reduce the effectiveness of hormonal contraceptives via induction of CYP 3A4; therefore, non-hormonal methods of contraception are recommended.[3,5]

Breastfeeding is not recommended due to the potential secretion into breast milk. Women should not breastfeed during treatment and for at least 1 week after the last dose.[3,5]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important[6,7].

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (76-93%, severe 7-29%); see paragraph following **Side Effects** table
	leukocyte decrease (11-13%)
	lymphocyte decrease (34-38%, severe 2-8%)
	platelet decrease (11%)
eye	retinal detachment (severe 5%)
	retinal vein occlusion (severe 5%)
	visual impairment (21-28%, severe 3%)
gastrointestinal	*emetogenic potential:* low[8]
	abdominal pain (10-23%, severe <1%)
	constipation (13-23%)
	diarrhea (11-18%, severe 1-2%)
	nausea (17-39%, severe <1%)
	vomiting (11%, severe <1%)
general disorders and administration site conditions	edema, peripheral (15-20%, severe <1%)
	fatigue (43-75%, severe 3-5%)
	flu like symptoms
immune system	anaphylaxis
infections and infestations	COVID-19 (13%, severe 2%)
	pneumonia (4%)
	sepsis (<1%); fatal events reported
	upper respiratory tract infection (21-23%)
	urinary tract infection (13%, severe 2%)
investigations	blood creatinine increase (11-67%, severe 5%)
	ALT increase (20-32%, severe 2%)
	AST increase (11-27%, severe 2%)
	calcium decrease (10-21%, severe 1%)
	glucose decrease (22%, severe 1%)
	glucose increase (34-56%, severe 5-7%)
	magnesium increase (31%, severe 2%)
	phosphate decrease (10-11%, severe 2%)
	potassium increase (13-29%, severe 3%)
	sodium decrease (31%, severe 2%)
	sodium increase (11%)
	weight increase (5-16%, severe 2%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
metabolism and nutrition	appetite decrease (13%, severe 1%)
	dehydration
musculoskeletal and connective tissue	arthralgia (18-21%)
	back pain (18%)
	muscle spasms (11%)
	musculoskeletal pain (34%, severe 1%)
	myalgia (16-25%, severe 2%)
nervous system	disturbance in attention (13%)
	dizziness (11-46%)
	headache (12-49%, severe <1%)
neoplasms	non-small cell lung cancer (1-10%)
	vulval cancer (1-10%)
psychiatric	anxiety (11%)
	insomnia (15%)
respiratory, thoracic and mediastinal	cough (11%)
	dyspnea (16-26%, severe 2%)
	hypoxia (2-29%, severe 10%); see paragraph following **Side Effects** table
	pleural effusion (2%)
skin and subcutaneous tissue	rash (8%)
vascular	***embolism*** (severe 5%); fatal events reported
	hemorrhage (9%, severe <1%); fatal events reported
	hypertension (6-15%, severe 3-10%)

Adapted from standard reference[1,3,5] unless specified otherwise.

Anemia is reported in the majority of patients. Some patients have developed severe anemia requiring transfusion. Median time to onset of all-grade anemia is 31 days (range: 1 day to 8.4 months). Monitor for anemia prior to treatment initiation and regularly during treatment. Withhold belzutifan for grade 3 or 4 events and permanently discontinue belzutifan for recurrent grade 3 or 4 events. The safety and efficacy of erythropoiesis stimulating agents for the treatment of anemia in patients with Von Hippel-Lindau disease has not been established.[3,5] Refer to protocol by which patient is being treated.

Hypoxia has been reported with belzutifan, including asymptomatic hypoxia and severe events requiring supplemental oxygen or hospitalization. Median time to onset is 31 days (range: 1 day to 21 months). Advise patients to promptly report any signs and symptoms of hypoxia. Monitor oxygen saturation with pulse oximetry prior to treatment initiation and regularly during treatment. Because asymptomatic hypoxia may occur, some patients may need to monitor oxygen saturation at home. Withhold belzutifan for grade 2 events as clinically indicated and for all grade 3 events. Following symptom resolution, consider resuming belzutifan at a reduced dose depending on the severity of the hypoxia. Discontinue treatment for recurrent hypoxia. Permanently discontinue belzutifan for grade 4 hypoxia.[3,5]

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INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
midazolam[5]	40% decrease in AUC and 24% decrease in C_{max} of midazolam	moderate induction of CYP 3A4 by belzutifan	if coadministration cannot be avoided, monitor for reduced efficacy of midazolam

Belzutifan is a moderate inducer of CYP 3A4. The plasma concentration of CYP 3A4 substrates may be reduced when coadministered with belzutifan, compromising their efficacy. This effect may be more pronounced in patients who are dual UGT 2B17 and CYP 2C19 poor metabolizers because the steady state AUC of belzutifan is projected to be up to 2-fold higher in these patients. Avoid coadministration with sensitive CYP 3A4 substrates for which minimal decreases in concentration may lead to therapeutic failure. Coadministration with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding.[3,5]

Belzutifan is a substrate of UGT 2B17 and CYP 2C19. Inhibitors of UGT 2B17 or CYP 2C19 may increase the plasma concentration of belzutifan. Monitor for belzutifan toxicity. Dose modification may be required.[3,5]

Belzutifan is a substrate of CYP 3A4, P-gp, OATP1B1, and OATP1B3; clinical significance is unknown.[3,5]

Belzutifan is an inhibitor of MATE2K; clinical significance is unknown.[3,5]

SUPPLY AND STORAGE:

Oral: Merck Canada Inc. supplies belzutifan as 40 mg film-coated tablets. Store at room temperature.[3]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

Oral:[3-5]
120 mg PO once daily (range 40-120 mg once daily)

Administer with food or on an empty stomach.

Concurrent radiation:
no information found

Dosage in myelosuppression:
modify according to protocol by which patient is being treated

Dosage in renal failure:
CrCl ≥ 30 mL/min: no adjustment required[3,5]
CrCl < 30 mL/min: no information found

$$\text{calculated creatinine clearance} = \frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$$

* For males N=1.23; for females N=1.04

Dosage in hepatic failure:
mild impairment (bilirubin ≤ 1.5 x ULN): no adjustment required[3,5]
moderate/severe impairment (bilirubin > 1.5 x ULN): no information found

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BC Cancer usual dose noted in ***bold, italics***

Dosage in dialysis: no information found

Children: safety and efficacy have not been established

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