PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

WELIREG®

belzutifan tablets

Tablets, 40 mg, Oral

Antineoplastic agent

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RECENT MAJOR LABEL CHANGES

1 Indications	07/2023
7 Warnings and Precautions	07/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

WELIREG® (belzutifan) is indicated for:

- the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated non-metastatic renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or non-metastatic pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.

Efficacy in patients with VHL disease-associated RCC, CNS hemangioblastomas, or pNET was based on objective response rate and duration of response in a single-arm study (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): There are limited data available on the use of WELIREG® in patients ≥ 65 years of age.

2 CONTRAINDICATIONS

- WELIREG® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Embryo-fetal toxicity (see 7 WARNING AND PRECAUTIONS, 16 NON-CLINICAL TOXICOLOGY)

- 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 hormonal contraceptives ineffective (see 9 DRUG INTERACTIONS)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG® (see 7 WARNING AND PRECAUTIONS, Special Populations).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of WELIREG® is 120 mg (three 40 mg tablets) administered orally once daily, with or without food (see 10.3 Pharmacokinetics). Tablets should be swallowed whole.
Treatment should continue until disease progression or unacceptable toxicity occurs.

Dose Modification Guidelines

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

Table 1. Recommended Dose Modifications

Adverse Reactions	Severity*	Dose Modification
Anemia (see 7 WARNINGS AND PRECAUTIONS)	Grade 3	• Withhold until resolved to ≤ Grade 2. • Resume at a reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of anemia.
	Grade 4	• Withhold until resolved to ≤ Grade 2. • Resume at a reduced dose (reduce by 40 mg) or permanently discontinue upon recurrence of Grade 4.
Hypoxia (see 7 WARNINGS AND PRECAUTIONS)	Grade 2	• Consider whether to continue or withhold until resolved. • If withheld, consider resuming at a reduced dose depending on severity and persistence of hypoxia.
	Grade 3	• Withhold until resolved. • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia.
	Grade 4	• Permanently discontinue.
Other Adverse Reactions (see 8 ADVERSE REACTIONS)	Grade 3	• Withhold dosing until symptoms improve to ≤ Grade 2. • Consider resuming at a reduced dose (reduce by 40 mg). • Permanently discontinue WELIREG® if Grade 3 adverse reaction recurs
	Grade 4	• Permanently discontinue.

*Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0

Pediatrics: Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥ 65 years of age): There are limited data available on the use of WELIREG® in patients ≥ 65 years of age. Based on population pharmacokinetic (PK) modeling, no dose adjustment is needed in patients ≥ 65 years of age (see 10 CLINICAL PHARMACOLOGY).

Renal Insufficiency: No dose adjustment is recommended in patients with mild (eGFR 60-89 mL/min/1.73 m^2) and moderate (eGFR 30-59 mL/min/1.73 m^2) renal insufficiency. WELIREG® has not been studied in patients with severe (eGFR 15-29 mL/min/1.73 m^2) renal insufficiency (see 10 CLINICAL PHARMACOLOGY).

Hepatic Insufficiency: No dose adjustment is recommended in patients with mild (total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 x ULN and any AST) hepatic insufficiency. WELIREG® has not been studied in patients with moderate or severe (total bilirubin >1.5 x ULN and any AST) hepatic insufficiency (see 10 CLINICAL PHARMACOLOGY).

UGT2B17 and CYP2C19 Genetic Polymorphism: No dose adjustment is recommended for patients who are dual UGT2B17 and CYP2C19 poor metabolizers (see 7 WARNINGS AND PRECAUTIONS, 10 CLINICAL PHARMACOLOGY).

4.4 Administration

WELIREG® is administered with or without food (see 10.3 Pharmacokinetics). Tablets should be swallowed whole. Treatment should continue until disease progression or unacceptable toxicity occurs.

4.5 Missed Dose

If a dose of WELIREG® is missed, it can be taken as soon as possible on the same day. The regular daily dose schedule for WELIREG® should be resumed the next day. Extra tablets should not be taken to make up for the missed dose. If vomiting occurs any time after taking WELIREG®, the dose should not be retaken. The next dose should be taken the next day.

5 OVERDOSAGE

There is no specific treatment for WELIREG® overdose. In cases of suspected overdose, if necessary, consider withholding WELIREG® and instituting supportive care. The highest dose of WELIREG® studied clinically was 240 mg total daily dose (120 mg twice a day or 240 mg once a day). Adverse reactions observed in patients receiving more than 120 mg once a day were generally similar to those observed at other doses. Dose-limiting toxicities included Grade 3 hypoxia (120 mg twice a day) and Grade 4 thrombocytopenia (240 mg once daily).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	Tablet / 40 mg / belzutifan	croscarmellose sodium, FD&C Blue #2 aluminum lake, hypromellose acetate succinate, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, colloidal silicon dioxide, talc and titanium dioxide.

Description
40 mg tablets of WELIREG®: blue, oval, film-coated tablet with "177" on one side. Available in bottle of 90 counts with desiccant.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Driving and Operating Machinery
No studies on the effects on the ability to drive and use machines have been performed. Dizziness and fatigue may occur following administration of WELIREG® which could influence the ability to drive or use machines (see 8 ADVERSE REACTIONS).

Hematologic
Anemia:
In a clinical trial (Study-004) with WELIREG® for the treatment of patients with VHL disease-associated RCC, anemia was reported in 55 patients (90.2%). Grade 3 anemia occurred in 7 patients (11.5%) (see 8 ADVERSE REACTIONS). Median time to onset of all Grade anemia events was 30 days (range: 1 day to 8.38 months). Of the 14 patients that were treated with an erythropoiesis-stimulating agent (ESA), 5 received treatment with both an ESA and blood transfusions, while 9 received treatment with an ESA alone. Patients received an ESA based on hemoglobin levels and physician discretion. In another clinical trial (Study-001) for the treatment of non-VHL disease-associated advanced solid tumors using the same dose of WELIREG®, anemia was reported in 44 patients (75.9%). Grade 3 anemia occurred in 16 patients (27.6%).

Monitor for anemia before initiation of and routinely throughout treatment with WELIREG®. For patients who develop Grade 3 anemia, withhold WELIREG® and treat according to standard medical practice until resolved to ≤ Grade 2. For recurrent Grade 3 anemia, discontinue WELIREG®. For patients who develop Grade 4 anemia, withhold WELIREG® and permanently discontinue for recurrent Grade 4 anemia (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment,10.2 Pharmacodynamics).

A significant baseline (≤ 120 g/L) effect was found for risk of developing ≥ Grade 3 anemia in a Phase 1 study.

Monitoring and Laboratory Tests
Monitor oxygen saturation with pulse oximetry before initiation of and regularly at follow up visits throughout treatment with WELIREG®. Some patients may experience asymptomatic hypoxia; at their discretion, health care providers may instruct patients to monitor oxygen saturation at home.

Monitor for anemia before initiation of and routinely throughout treatment with WELIREG®.

Reproductive Health: Female and Male Potential
See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7.1.1 Pregnant Women

- **Fertility:**
  No data on the effects of WELIREG® on fertility in humans are available. Based on findings in animals, WELIREG® may impair fertility in males and females of reproductive potential (see 16 NON-CLINICAL TOXICOLOGY). The reversibility of the effect on fertility is unknown. Advise patients of this potential risk. Family planning should be discussed with patients as appropriate.

- **Teratogenic Risk**
  Embryo-Fetal Toxicity:
  Based on findings in animals, WELIREG® may cause fetal harm, including fetal loss, in humans (see 16 NON-CLINICAL TOXICOLOGY). Advise females of reproductive potential to use highly effective non-hormonal contraceptive methods during treatment with WELIREG® and for at least 1 week after the last dose due to the potential risk to the fetus. Use of WELIREG® may reduce the effectiveness of hormonal contraceptives (see 9.4 Drug-Drug Interactions). Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG®.

  Advise male patients with female partners of reproductive potential to use highly effective contraceptive methods during treatment with WELIREG® and for at least 1 week after the last dose (see 7 WARNINGS AND PRECAUTIONS, Special Populations and 16 NON-CLINICAL TOXICOLOGY).

Respiratory
Hypoxia:
In a clinical trial (Study-004) with WELIREG® for the treatment of patients with VHL disease-associated RCC, Grade 3 hypoxia occurred in 1 patient (1.6%) (see 8 ADVERSE REACTIONS). In a Phase 1 clinical trial (Study-001) for the treatment of non-VHL disease-associated advanced solid tumors using the same dose of WELIREG®, hypoxia occurred in 17 patients (29.3%%), Grade 3 hypoxia occurred in 9 patients (15.5%).

Monitor oxygen saturation with pulse oximetry before initiation of and regularly at follow up visits throughout treatment with WELIREG®. Some patients may experience asymptomatic hypoxia; at their discretion, health care providers may instruct patients to monitor oxygen saturation at home. For Grade 2 hypoxia, treat according to standard medical practice and consider whether to continue or withhold WELIREG® treatment. If withheld, consider resuming at a reduced dose depending on severity of hypoxia. For Grade 3 hypoxia, withhold WELIREG® until resolved and treat according to standard medical practice. Resume at reduced dose or discontinue depending on the severity of hypoxia. For recurrent hypoxia, discontinue treatment. For Grade 4 hypoxia, permanently discontinue treatment (see 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment).

7.1 Special Populations

7.1.1 Pregnant Women

Based on findings in animal studies, WELIREG® may cause fetal harm, including fetal loss, when administered to a pregnant woman (see 16 NON-CLINICAL TOXICOLOGY). There are no available data on the use of WELIREG® in pregnant women to evaluate drug-associated risk. Advise females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown.

For information on contraception for patients who are females of child bearing potential or male patients, please refer to 7 WARNINGS AND PRECAUTIONS, Reproductive Health: Female and Male Potential.

7.1.2 Breast-feeding

It is unknown if WELIREG® or its metabolites are excreted in human milk, and there are no data on their effects on the breastfed child, or on milk production. Precaution should be exercised because many drugs can be excreted in human milk. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with WELIREG® and for at least 1 week after the last dose.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Safety and effectiveness of WELIREG® in pediatric patients under 18 years of age have not been established.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): Based on population PK modeling, no dosage adjustment is recommended in geriatric patients (see 10 CLINICAL PHARMACOLOGY). There were 2 (3.3%) patients with VHL disease-associated RCC ≥65 years of age in the Phase 2 Study-004 (see 14 CLINICAL TRIALS). There were 24 (41.4%) patients with non-VHL disease-associated advanced solid tumors ≥65 years of age in the Phase 1 Study-001. Based on limited numbers of patients ≥65 years of age, the safety profile in these patients did not appear to differ from that of patients <65 years of age.

7.1.5 Renal insufficiency

WELIREG® has not been studied in patients with severe renal insufficiency (see 4 DOSAGE AND ADMINISTRATION, Renal Insufficiency and 10.3 Pharmacokinetics)

7.1.6 Hepatic insufficiency

WELIREG® has not been studied in patients with moderate or severe hepatic insufficiency (see 4 DOSAGE AND ADMINISTRATION, Hepatic Insufficiency and 10.3 Pharmacokinetics)

7.1.7 UGT2B17 and CYP2C19 Genetic Polymorphism

WELIREG® is primarily metabolized by UGT2B17 and CYP2C19. Individuals who are dual UGT2B17 and CYP2C19 poor metabolizers are projected to have up to 2.3-fold higher WELIREG® exposures (steady state AUC0-24hr) compared to a UGT2B17 intermediate metabolizer or CYP2C19 non-poor metabolizer, for the recommended dose. No dose adjustment is recommended (see 10.3 Pharmacokinetics).

Estimated frequencies of CYP2C19 and UGT2B17 poor metabolizers in certain populations are listed below:

UGT2B17 poor metabolizers: 15% of Caucasians, 11% of Latinos, 6% of African Americans, 38% of South Asians, and 70% of East Asians

CYP2C19 poor metabolizers: 2% of Caucasians, 1% of Latinos, 5% of African Americans, 8% of South Asians, and 13% of East Asians

Dual UGT2B17 and CYP2C19 poor metabolizers: 0.3% of Caucasians, 0.1% of Latinos, 0.3% of African Americans, 3% of South Asians, and 9% of East Asians

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following clinically significant adverse reactions are discussed elsewhere in the labeling (see 7 WARNINGS AND PRECAUTIONS):

- Anemia (see 7 WARNINGS AND PRECAUTIONS)
- Hypoxia (see 7 WARNINGS AND PRECAUTIONS)

The safety of WELIREG® was evaluated in an open-label single-arm Phase 2 clinical study (Study-004), in 61 patients with VHL disease-associated RCC and who did not require immediate surgery. Enrolled participants included those with other VHL disease-associated tumours such as pancreatic lesions, pancreatic neuroendocrine tumours (pNETs), central nervous system hemangioblastomas (CNS HB) and retinal hemangioblastomas.Patients were treated with 120 mg WELIREG® once daily. The median duration of exposure to WELIREG® was 37.3 months (range 1.9 to 46.1 months) with 90% exposed for 18 months or longer.

Treatment-Emergent Adverse Events

In the pivotal Study-004, a treatment-emergent adverse event (TEAE) was reported by all 61 patients who received WELIREG®. The most common TEAEs (incidence ≥20%) under treatment with WELIREG® were anemia (90.2%), fatigue (73.8%), headache (47.5%), dizziness (45.9%), nausea (39.3%), dyspnea (26.2%), myalgia (24.6%), constipation (23.0%), arthralgia (21.3%) and vision blurred (21.3%).

Grade ≥3 TEAE occurred in 44.3% of patients, with Grade 3, Grade 4, and Grade 5 TEAEs observed in 36.1%, 4.9%, and 3.3%, respectively. The most common Grade ≥3 TEAEs were anemia (11.5%), hypertension (9.8%), and fatigue (4.9%). There were 3 (4.9%) Grade 4 TEAEs (embolism, retinal detachment, and retinal vein occlusion) and 2 (3.3%) Grade 5 TEAEs (suicide attempt and toxicity to various agents).

Serious TEAE were reported in 29.5% of patients; the only SAEs reported by more than 1 participant were hemorrhage intracranial and embolism (2 participants with VHL-CNS HB [3.3%] each).

The most frequently (≥3%) reported TEAEs leading to treatment interruption were fatigue (11.5%), nausea (9.8%), headache (6.6%), dizziness (4.9%), influenza-like illness (4.9%), abdominal pain (3.3%), anemia (3.3%), COVID-19 (3.3%), haemorrhage intracranial (3.3%), syncope (3.3%) and vomiting (3.3%).

The most common TEAE resulting in dose reduction of WELIREG® were fatigue (8.2%) and anemia (3.3%). No other AEs that led to dose reduction were reported by more than 1 patient.
TEAE resulted in the permanent discontinuation of WELIREG® for 4 patients (6.6%) (Grade 1 dizziness, Grade 2 hemorrhage intracranial, Grade 5 toxicity to various agents, Grade 5 suicide attempt).

8.2 Clinical Trial Adverse Reactions
Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of WELIREG® was evaluated in all 61 patients enrolled in the pivotal single-arm Phase 2 clinical study (Study-004) with VHL disease-associated non-metastatic RCC who received at least one dose of WELIREG® monotherapy at a dose of 120 mg. In Study-004, the median duration of exposure was 37.3 months (range 1.9 to 46.1 months). The median age was 41 years (range 19 to 66 years), with 3.3% of patients ≥ 65 years of age. Treatment-emergent adverse events that were reported in ≥10% of patients are listed in the Table 3.

Table 3 – Treatment-Emergent Adverse Events Occurring in ≥ 10 % of Patients Treated with WELIREG® (Study-004)

	WELIREG® N= 61	
	All Grades n (%)	**Grade 3-4 n (%)**
Blood and lymphatic disorders		
Anemia	55 (90)	7 (11)
Eye Disorders		
Visual impairment[†]	17 (28)	2 (3)
Gastrointestinal disorders		
Nausea	24 (39)	0
Constipation	14 (23)	0
Abdominal pain[‡]	14 (23)	0
Diarrhea	11 (18)	1 (2)
Vomiting	7 (11)	0
General disorders and administration site disorders		
Fatigue[§]	46 (75)	3 (5)
Edema peripheral	9 (15)	0

	WELIREG® N= 61	
Infections		
COVID-19[a]	8 (13)	1 (2)
Upper respiratory tract infections[¶]	14 (23)	0
Urinary tract infection	8 (13)	1 (2)
Investigations		
Alanine aminotransferase increased	12 (20)	0
Weight increased	10 (16)	1 (2)
Aspartate aminotransferase increased	7 (11)	0
Blood creatinine increased	7 (11)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (21)	0
Back pain	11 (18)	0
Myalgia	15 (25)	1 (2)
Muscle spasms	7 (11)	0
Nervous system disorders		
Headache[#]	30 (49)	0
Dizziness[þ]	28 (46)	0
Disturbance in attention	8 (13)	0
Psychiatric Disorder		
Insomnia	9 (15)	0
Anxiety	7 (11)	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea	16 (26)	1 (2)
Cough	7 (11)	0
Vascular disorders		
Hypertension	9 (15)	6 (10)

[†] includes visual impairment, vision blurred, retinal vein occlusion and retinal detachment
[‡] includes abdominal discomfort, abdominal pain, abdominal pain upper and abdominal pain lower
[§] includes fatigue and asthenia
[¶] includes bronchitis, sinusitis, upper respiratory tract infection and viral upper respiratory tract infection
[#] includes headache and migraine
[þ] includes dizziness and vertigo
[a] includes COVID-19, COVID-19 pneumonia, and post-acute COVID-19 syndrome

In a clinical study (Study-004) with WELIREG® for the treatment of patients with VHL disease-associated RCC, Grade 3 hypoxia occurred in 1 patient (1.6%). This case of hypoxia occurred within 2 months of treatment initiation in a patient with previously undiagnosed restrictive lung disease and was asymptomatic. This patient did not receive supplemental oxygen and was managed with dose reduction to 80 mg QD with no recurrence of hypoxia. In another clinical study (Study-001) for the treatment of non-VHL disease-associated advanced solid tumors using the same dose of WELIREG®, hypoxia occurred in 18 patients (31%), with Grade 3 hypoxia occurring in 12 patients (20.7%).

8.3 Less Common Clinical Trial Adverse Reactions

The following terms are treatment-emergent adverse events reported at an incidence of ≥1% and <10%.

Blood and lymphatic system disorder: hypotransferrinaemia, lymphadenopathy

Cardiac disorders: sinus bradycardia, pericardial effusion, sinus tachycardia, angina pectoris, coronary artery dissection, left ventricular dysfunction, tachycardia, palpitations, atrial enlargment

Ear and labyrinth disorders: tinnitus, external ear pain, ear pain, eustachian tube dysfunction, excessive cerumen production, hypoacusis, mastoid effusion, middle ear effusion, ear discomfort, external ear inflammation, middle ear inflammation

Endocrine disorders: hypothyroidism, adrenal insufficiency

Eye Disorders: dry eye, lacrimation increased, diplopia, conjunctival hemorrhage, eye irritation, photophobia, vitreous floaters, blepharitis, myopia, ocular discomfort, periorbital oedema, presbyopia, retinal-hemorrhage, retinal vascular disorder, eye pain, vitreous hemorrhage

Gastrointestinal disorders: stomatitis, abdominal distension, gastritis, oral pain, aphthous ulcer, colitis, mouth cyst, dry mouth, dyspepsia, gastro esophageal reflux disease, hemorrhoidal hemorrhage, hemorrhoids, lip edema

General disorders and administration site conditions: non-cardiac chest pain, chills, malaise, gait disturbance, complication associated with device, localised oedema, drug interaction, feeling abnormal, generalised oedema, peripheral swelling, sensation of foreign body, temperature intolerance, chest discomfort, pain, nodule, pyrexia, chest pain, influenza like illness

Hepatobiliary disorders: biliary colic

Immune system disorders: seasonal allergy, contrast media allergy, hypersensitivity, anaphylactic reaction

Infections and infestations: conjunctivitis, otitis media, influenza, cystitis, diverticulitis, rhinitis, viral infection, hordeolum, herpes zoster, body tinea, borrelia infection, eye infection, folliculitis, gastroenteritis viral, helicobacter infection, herpes simplex reactivation, nail infection, nasopharyngitis, respiratory tract infection, scrotal infection, tonsillitis streptococcal, urinary tract infection enterococcal, cellulitis, otitis media chronic, pneumonia, rash pustular

Injury, poisoning and procedural complications: fall, contusion, arthropod sting, exposure to communicable disease, face injury, incision site pain, muscle rupture, ocular procedural complication, rib fracture, skin laceration, thermal burn, toxicity to various agents, ligament sprain, procedural pain, spinal fracture

Investigations: white blood cell count decreased, neutrophil count decreased, blood cholesterol increased, reticulocyte count decreased, lymphocyte count decreased, platelet count decreased, blood bilirubin increased, amylase increased, blood iron decreased, epinephrine increased, glomerular filtration rate decreased, nitrite urine present, right ventricular systolic pressure increased, weight decreased, blood alkaline phosphatase increased, intraocular pressure increased, lipase increased, SARS-CoV-2 test positive

Metabolism and nutrition disorders: decreased appetite, hyperglycaemia, hypermagnesaemia, hypoglycaemia, dehydration, hyperkalaemia, hypophosphataemia, hyponatraemia, vitamin D deficiency, hypokalemia, diabetes mellitus, iron deficiency

Musculoskeletal and connective tissue disorders: neck pain, muscular weakness, musculoskeletal chest pain, musculoskeletal pain, pain in jaw, joint effusion, flank pain, pain in extremity

Neoplasms benign, malignant and unspecified: vulval cancer, non-small cell lung cancer

Nervous system disorders: dysgeusia, syncope, tremor, hyperaesthesia, hypoaesthesia, peripheral sensory neuropathy, somnolence, presyncope, depressed level of consciousness, seizure, cognitive disorder, dysaesthesia, memory impairment, hemorrhage intracranial, loss of consciousness, neuralgia, sciatica, paraesthesia, aphasia, dysarthria, hemiparaesthesia, peroneal nerve palsy, restless legs syndrome

Product issues: device dislocation

Psychiatric disorders: depressed mood, dysphoria, major depression, mood altered, depression, attention deficit hyperactivity disorder, hypnopompic hallucination, suicide attempt

Renal and urinary disorders: pollakiuria, micturition urgency, renal pain, acute kidney injury, nocturia, haematuria, urinary incontinence, bladder spasm, nephrolithiasis, urine flow decreased

Reproductive system and breast disorders:, pelvic pain, dysmenorrhoea, menopausal symptoms, vaginal lesion, vulvovaginal dryness, azoospermia, heavy menstrual bleeding, abnormal uterine bleeding, breast mass, erectile dysfunction, gynecomastia, menstruation irregular, ovarian cyst, testicular atrophy

Respiratory, thoracic and mediastinal disorders: upper-airway cough syndrome, hypoxia, dysphonia, epistaxis, tonsillar hypertrophy, oropharyngeal pain, nasal congestion, rhinitis allergic

Skin and subcutaneous tissue disorders: pruritus, rash maculo-papular, rash, decubitus ulcer, dermatitis acneiform, skin disorder, skin exfoliation, alopecia, blister, dermatitis contact,

mucocutaneous rash, nail ridging, onycholysis, rash pruritic, skin discolouration, skin odour abnormal, sweat gland disorder, urticaria, xeroderma, dry skin, petechia

Surgical and medical procedures: cholecystectomy

Vascular disorders: hypotension, orthostatic hypotension, hot flush, embolism

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings:

Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4 Select Laboratory Abnormalities (>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	67	0
Increased glucose	56	7
Increased potassium	13	0
Increased ALT	21	0
Increased AST	18	0
Decreased calcium (corrected)	11	0
Decreased phosphate	11	2
Magnesium increase	31	2
Sodium increase	11	0
Hematology		
Decreased hemoglobin	93	10
Decreased leukocytes	13	0
Decreased platelets	11	0
Lymphocytes Decreased (Lymphocyte count decrease)	38	2

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

8.5 Post-Market Adverse Reactions

Not applicable.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro and pharmacogenomic studies indicate that WELIREG® is metabolized by UGT2B17 and by CYP2C19.

In Vitro Assessment of Drug Interactions

WELIREG® is a substrate of UGT2B17, CYP2C19 and CYP3A4. WELIREG® is not an inhibitor of CYP enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4). WELIREG® is a weak substrate of P-gp, OATP1B1 and OATP1B3. WELIREG® does not induce CYP1A2 or CYP2B6; however, WELIREG® is a moderate CYP3A4 inducer. WELIREG® does not inhibit the transporters P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or MATE1, but does inhibit MATE2K. Inhibition of OCT1 cannot be ruled out.

9.4 Drug-Drug Interactions

Effects of WELIREG® on Other Drugs

In vitro studies have shown that WELIREG® induces CYP3A4. Based on physiologically based pharmacokinetic (PBPK) model analyses, co-administration of WELIREG® 120 mg once daily dose with midazolam (a sensitive CYP3A4 substrate) is predicted to decrease midazolam AUC by approximately 50-70%. Other compounds that are CYP3A4 substrates (including hormonal contraceptives) may have decreased plasma concentrations and reduced efficacy when co-administered with WELIREG®.

Effects of Other Drugs on WELIREG®

Based on PBPK model analyses, co-administration with inhibitors of UGT2B17 or CYP2C19 is expected to increase plasma exposure of WELIREG®. Dose adjustment is not recommended on co-administration with inhibitors of UGT2B17 or CYP2C19.

9.5 Drug-Food Interactions

A high fat, high-calorie meal delayed WELIREG® Tmax but had no clinically meaningful effect on exposure (see 10.3 Pharmacokinetics, Food Effect). Interactions with other foods have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α), a transcription factor that plays a role in oxygen sensing by regulating genes that promote adaptation to hypoxia. Under normal oxygen levels, HIF-2α is targeted for ubiquitin-proteasomal degradation by VHL protein. Lack of functional VHL protein results in stabilization and accumulation of HIF-2α. Upon stabilization, HIF-2α translocates into the nucleus and interacts with hypoxia-inducible factor 1 beta (HIF-1β) to form a transcriptional

complex that regulates expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumor growth. Belzutifan binds to HIF-2α and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1β interaction, leading to reduced expression of HIF-2α target genes. In vivo, belzutifan demonstrated anti-tumor activity in mouse xenograft models of renal cell carcinoma.

10.2 Pharmacodynamics

Treatment with WELIREG® in patients with VHL disease-associated RCC and in those with non-VHL disease-associated advanced solid tumors resulted in reductions in plasma levels of erythropoietin (EPO) which were observed to be dose- and/or exposure-dependent up to 120 mg once daily. Peak EPO suppression occurred at 2 weeks of treatment (mean of approximately 60% decrease from baseline). Mean EPO levels for VHL disease-associated RCC patients gradually returned to baseline values after 12 weeks of treatment. The incidence of Grade 3 anemia increased with higher exposure in patients with baseline hemoglobin levels <120 g/L (see 7 WARNINGS AND PRECAUTIONS).

Cardiac Electrophysiology

At the recommended dose (120 mg once daily) for WELIREG®, there were no clinically relevant effects on the QTc interval. Based on concentration-QTc modeling in Study-004, the predicted mean change from baseline in QTcF (ΔQTcF) was 2.6 msec (90% CI: 0.67 to 4.43) for the dose of 120 mg daily (geometric mean Cmax of 1.39 mcg/mL). These results were aligned with the by-time-point analysis showing the mean ΔQTcF between −5.3 msec at Week 9, pre-dose, and 5.7 msec at Week 1, 2 hours post-dose. The 90% 2-sided upper confidence bound for ΔQTcF was below 10 msec at all time points.

10.3 Pharmacokinetics

Based on a population PK model analysis, the predicted steady-state geometric mean for Cmax and $AUC_{0\text{-}24hr}$ for 120 mg once daily belzutifan in 61 patients with VHL disease-associated RCC are shown in Table 5. Steady state is reached after approximately 3 days of once daily dosing. Plasma Cmax and AUC increased proportionally from 20 mg up to the recommended dose of 120 mg.

Table 5 - Predicted Steady State Pharmacokinetic Parameters in VHL-RCC patients

	C_{max} (mcg/mL)	**$AUC_{0\text{-}24hr}$ (mcg •hr/mL)**
Predicted steady state geometric mean (CV%)	1.3 (42.2%)	16.7 (52.3%)

Absorption

Following oral administration of 120 mg of WELIREG®, peak plasma concentrations occurred at 1 to 2 hours postdose (median Tmax).

A high-fat, high-calorie meal delayed time to peak WELIREG® concentration by approximately 2 hours and had no clinically meaningful effect on Cmax (decrease of 35%) or AUC. Therefore, WELIREG® can be taken without regard to food.

Distribution:

The mean steady-state volume of distribution of WELIREG® following an oral dose is 130 L. Plasma protein binding of WELIREG® is 45%. The blood-to-plasma concentration ratio of WELIREG® is 0.88.

Metabolism:
WELIREG® is primarly metabolized by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4. WELIREG® glucuronide conjugate, a major human metabolite does not inhibit HIF-2α, and has low potential to be a perpetrator of drug interactions. Both UGT2B17 and CYP2C19 display genetic polymorphisms (see 10.3 Pharmacokinetics, Special Populations and Conditions).

Elimination
The mean clearance of WELIREG® is 7.3 L/hr and the mean elimination half-life is 14 hrs.

Metabolism is expected to be the major route of elimination. Renal excretion is not a major route of elimination.

Special Populations and Conditions
Based on population PK modeling, age (19-84 years), sex, ethnicity, race, body weight (42 kg-166 kg), food, mild (eGFR 60-89 mL/min/1.73 m^2 estimated by MDRD) to moderate (eGFR 30-59 mL/min/1.73 m^2) renal insufficiency, and mild hepatic insufficiency [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 x ULN and any AST] do not have a clinically meaningful effect on the pharmacokinetics of WELIREG®. Potential differences in exposure across races are possible due to different frequencies of metabolizing enzymes, UGT2B17 and CYP2C19.

- **Pediatrics:** No studies with WELIREG® have been performed in pediatric patients.

- **Geriatrics:** There are limited data available on the use of WELIREG® in patients aged 65 years and over. Based on population PK modeling, age (19-84 years), does not have a clinically meaningful effect on the pharmacokinetics of WELIREG®.

- **Renal insufficiency:** No clinically relevant increase in predicted exposure (AUC) was observed for patients with mild (eGFR 60-89 mL/min/1.73 m^2 estimated by MDRD) or moderate (eGFR 30-59 mL/min/1.73 m^2) renal impairment vs Normal (as evaluated by eGFR) based on population PK modeling. No dose adjustment is recommended for patients with mild or moderate renal insufficiency. The pharmacokinetics of WELIREG® have not been studied in patients with severe renal impairment (see 4 DOSAGE AND ADMINISTRATION).

- **Hepatic insufficiency:** No clinically relevant increase in predicted exposure (AUC) was observed for patients with mild hepatic impairment [total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN or total bilirubin >1 to 1.5 x ULN and any AST] vs Normal based on population PK modeling. No dose adjustment is recommended for patients with mild hepatic insufficiency. The pharmacokinetics of WELIREG® have not been studied in patients with moderate or severe hepatic impairment (see 4 DOSAGE AND ADMINISTRATION).

- **UGT2B17 and CYP2C19 Genetic Polymorphism:** WELIREG® is primarily metabolized by UGT2B17 and CYP2C19. Poor metabolizers are individuals who are considered to have no enzyme activity.

Based on population PK modeling, VHL disease-associated RCC patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolizers, are projected to have 1.5-, 1.6-, or 2.3-fold higher WELIREG® exposures (steady state AUC0-24hr), respectively, compared to UGT2B17 intermediate metabolizers and CYP2C19 non-poor metabolizers, for the recommended dose. No dose adjustment is recommended based on exposure-response analyses for efficacy and safety.

11 STORAGE, STABILITY AND DISPOSAL

Store WELIREG® at room temperature, between 15°C to 30°C.

PART II: SCIENTIFIC INFORMATION

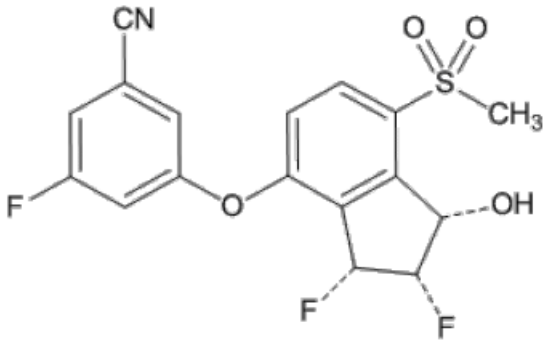
13 PHARMACEUTICAL INFORMATION

Drug Substance
Proper/Common name: Belzutifan

Chemical name: 3-[[(1S,2S,3R)-2,3-Difluoro-2,3-dihydro-1-hydroxy-7-(methylsulfonyl)-1H-inden-4-yl]oxy]-5-fluorobenzonitrile

Molecular formula and molecular mass: $C_{17}H_{12}F_3NO_4S$; 383.34 Daltons

Structural formula:



Physicochemical properties: 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.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Von Hippel-Lindau (VHL) disease-associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas and pancreatic neuroendocrine tumours (pNETs)
The efficacy of WELIREG® was investigated in Study-004 (NCT03401788), an open-label Phase 2 clinical trial in 61 patients with VHL disease who had at least one measurable solid tumor (as defined by RECIST v1.1) localized to the kidney and who did not require immediate surgery. Enrolled participants included those with other VHL disease-associated tumours such as pancreatic lesions, pancreatic neuroendocrine tumours (pNETs), central nervous system (CNS) hemangioblastomas and retinal hemangioblastomas, based on central independent review committee (IRC). Of the 61 partipicants, 50 had CNS hemangioblastomas and 22 had pNET. Patients received WELIREG® at a dose of 120 mg once daily. Patients were evaluated radiologically approximately 12 weeks after initiation of treatment and every 12 weeks thereafter. Treatment was continued until progression of disease or unacceptable toxicity. The study excluded patients who had any evidence of metastatic disease, either RCC or other VHL disease-associated tumors, an immediate need for surgical intervention for tumor treatment, any major surgical procedure completed within 4 weeks prior to study enrollment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease-associated RCC.

The study population characteristics were: median age of 41 years, 3.3% age 65 or over; 52.5% male; 90.2% White; and 82.0% had an ECOG PS of 0 and 16.4% had an ECOG PS of 1. Seventy-seven percent of patients had prior RCC surgical procedures.

The major efficacy endpoint for the treatment of VHL disease-associated RCC was overall response rate (ORR) measured by Integrated Radiology and Oncology Assessment (IRO) assessment using RECIST v1.1 as assessed by IRC. Additional efficacy endpoints included duration of response (DoR) and time to response (TTR). Radiographic endpoints were assessed by IRC using RECIST v1.1.

Table 6 - Summary of trial design and study demographic (Study-004)

Study #	Study design	Dosage, route of administration	Study subjects (n)	Mean age (Range)	Sex
MK-6482-004 (Study-004)	Open-label	120 mg, oral	61	41 (19, 66)	Male: 32 (52.5%) Female: 29 (47.5 %)

Table 7 summarizes the efficacy results for VHL disease-associated RCC tumors in Study-004 after a median follow-up of 37.7 months (range: 4.2, 46.1).

Table 7 – Efficacy Results for WELIREG® for VHL Disease-Associated RCC Tumors (Study-004)

Primary Endpoints	WELIREG® 120mg daily N= 61
Overall Response Rate * n (%) (95% CI)	39 (63.9%) (50.6%, 75.8%)
Complete response	4 (6.6%)
Partial response	35 (57.4%)
Duration of Response‡	
Median in months (range)	Not reached (5.4+, 35.8+)
% (n) with duration ≥ 12 months	35 (100.0%)
Time to response	
Median in months (range)	11.1 (2.7, 30.5)

*Response: Best objective response as confirmed complete response or partial response
‡ Based on Kaplan-Meier estimates
+ Denotes ongoing response
Results presented in this table reflect a median follow-up of 37.7 months (range: 4.2, 46.1)

Efficacy endpoints for the treatment of other VHL disease-associated tumors included ORR, and response duration, as assessed by IRC using RECIST v1.1. These results are shown in Table 8.

Table 8: Efficacy Results for WELIREG® for Other VHL Disease-Associated Tumors

	WELIREG® 120 mg daily N=61	
Endpoint	**Patients with Evaluable pNET N=22**	**Patients with Evaluable CNS Hemangioblastomas[¥] N=50**
Overall Response Rate* n (%) (95% CI)	20 (90.9%) (70.8%, 98.9%)	22 (44%) (30.0%, 58.7%)
Complete response	7 (31.8%)	4 (8.0%)
Partial response	13 (59.1%)	18 (36.0%)
Duration of Response[‡]		
Median in months (range)	Not reached (11+, 37.3+)	Not reached (3.7+, 38.7+)
% (n) with duration ≥ 12 months	19 (100%)	16 (90%)
Time to response		
Median in months (range)	8.2 (2.5, 16.4)	5.4 (2.3, 33.1)

*Response: Best objective response as confirmed complete response or partial response
‡ Based on Kaplan-Meier estimates
+ Denotes ongoing response
[¥] Reflect analysis with tumor measurements that included both solid tumour and associated cystic components if present.
Results presented in this table reflect a median follow-up of 37.7 months (range: 4.2, 46.1)

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:
The toxicologic potential of belzutifan was assessed via oral treatment in Sprague-Dawley rats and Beagle dogs. Reduction in red blood cell parameters (red blood cell counts, hemoglobin and hematocrit) and reticulocytes were observed in both animal models at exposure levels lower than the human exposure at the recommended dose of 120 mg daily.

In a repeat dose toxicity study where rats were dosed 2, 6, 20 or 200 mg/kg/day for 91 days, belzutifan caused irreversible testicular atrophy/degeneration at ≥ 0.2 times the exposure observed in humans (based on AUC) at the clinical recommended dose of 120 mg daily (see 16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). An increase in hepatocellular necrosis was also recorded across all dosing level, however, it was considered incidental. The NOAEL was considered to be 2 mg/kg/day (approximately 0.1 times the human exposure) in males and 200 mg/kg/day (approximately 1 time the human exposure based on AUC) in female rats.

In a 13-week study, dogs received 1, 5, or 30 mg/kg/day of belzutifan. No testicular toxicity was observed at any dose. Decreases in thymus weight that correlated with the microscopic finding of lymphoid hypocellularity in the thymus were noted in females and high dosed males, but were considered incidental. The NOAEL was determined to be 30 mg/kg/day, equivalent to 2 times the exposure (AUC) expected in patients at the 120 mg daily dose.

Carcinogenicity:
Carcinogenicity studies have not been conducted with belzutifan.

Genotoxicity:
Belzutifan was not mutagenic in the in vitro Ames bacterial cell assay or the in vitro micronucleus assay. Belzutifan was not genotoxic in an in vivo rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicology:
Fertility studies with belzutifan have not been conducted. In repeat-dose toxicity studies up to 3-month duration, WELIREG®-related findings included degeneration/atrophy of male reproductive organs in rats administered ≥2 mg/kg/day (approximately 0.1 times the human exposure at the recommended dose of 120 mg daily). Some of these findings were not reversible and were associated with decreased sperm count, motility and abnormal sperm morphology, therefore impairment of male fertility in rats is expected.

There were no findings in female reproductive organs in either rat or dog 3-month studies. However, in an animal embryo-fetal development study, oral administration of WELIREG® to pregnant rats during the period of organogenesis at dose levels of 6, 60, or 200 mg/kg/day (maternal plasma systemic exposures ≥0.2 times the human exposure based on area under the curve (AUC) at the recommended dose of 120 mg daily) resulted in embryo-fetal lethality (post-implantation loss), reduced fetal body weights, fetal rib malformations, and reduced skeletal ossification.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

WELIREG®

belzutifan tablets

Read this carefully before you start taking **WELIREG®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **WELIREG®**.

Serious Warnings and Precautions

- WELIREG® can harm your unborn baby.
- Your healthcare professional will do a pregnancy test before you start taking WELIREG®.
- Use birth control that does not contain hormones while you take this medicine. This is because WELIREG® may cause hormonal birth control to not work. Keep using the birth control for at least 1 week after your last dose.

See the "*Other warnings you should know about: Pregnancy information for Females and Males*" section for more information.

What is WELIREG® used for?

WELIREG® is used to treat adults with von Hippel-Lindau (VHL) disease who need treatment for, and do not require surgery right away for:

- kidney cancer that has not spread to other parts of the body;
- tumors in the brain and spinal cord called central nervous system hemangioblastomas; or
- a type of pancreatic cancer called pancreatic neuroendocrine tumors, that has not spread to other parts of the body.

How does WELIREG® work?

WELIREG® blocks the action of a protein that causes your cancer to grow.

What are the ingredients in WELIREG®?

Medicinal ingredient: Belzutifan.

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

WELIREG® comes in the following dosage forms:

- Tablets, 40 mg

Do not use WELIREG® if:

- you are allergic to WELIREG® or any of the other ingredients of this medicine or container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take WELIREG®. Talk about any health conditions or problems you may have, including if you:

- have breathing or lung problems

- have low levels of oxygen in your blood
- have heart problems / heart disease
- have low levels of red blood cells (anemia)

Other warnings you should know about:

Check-ups and testing: You will have regular visits with your healthcare professional, before, during and at the end of your treatment. They will:

- Check for **hypoxia (low body oxygen levels)** using a pulse oximeter. WELIREG® may cause low oxygen levels in your body. Your healthcare professional may ask you to monitor your oxygen levels at home as well.
- Do blood tests to check for:
    - **Anemia (low red blood cell levels):** WELIREG® may cause low red blood cell levels in your blood.

See the "Serious side effects and what to do about them" table, below, for more information on these and other serious side effects.

Pregnancy information for Females and Males

Female Patients

- If you are pregnant, able to get pregnant, or plan to become pregnant, talk to your healthcare professional.
- WELIREG® can harm your unborn baby and cause a miscarriage.
- If you are able to become pregnant:
    - Your healthcare professional will do a pregnancy test before you start taking WELIREG®.
    - Avoid becoming pregnant while taking WELIREG®.
    - Use birth control while you take this medicine. Keep using birth control for at least 1 week after your last dose. The birth control methods you use must not contain hormones because WELIREG® may cause these types of birth control to not work. Ask your healthcare professional about birth control methods that may be right for you during this time.
    - Tell your healthcare professional right away if you become pregnant or think you may be pregnant during your treatment with WELIREG®.
- If you are breastfeeding or plan to breastfeed, talk to your healthcare professional.
    - It is not known if WELIREG® passes into your breast milk. It may harm your baby.
    - Do not breastfeed while you are taking WELIREG® and for at least 1 week after your last dose.

Male Patients

- Avoid fathering a child while you are taking WELIREG®.
- During your treatment with WELIREG®, use a condom each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Continue using condoms for at least 1 week after your last dose.
- If during treatment with WELIREG®, your partner becomes pregnant or thinks she maybe pregnant, tell your healthcare professional right away.

Fertility

- WELIREG® may cause fertility problems in females and males. It is unknown if these problems would be permanent. If you want to have children, talk to your healthcare professional before taking WELIREG®.

Driving and using machines: Before you drive or do tasks that require special attention, wait until you know how you respond to WELIREG®. You may feel dizzy or tired after taking WELIREG®. If this happens, do not drive or use tools or machines until you no longer feel dizzy or tired.

Children and Adolescents (less than 18 years of age): It is not known if WELIREG® is safe and effective for use in people under 18 years old. Do not give this medicine to children and adolescents under 18 years old.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with WELIREG®:

- Some medicines may increase the risk of side effects with WELIREG®, like:
    - imatinib (used to treat cancer)
    - fluconazole (used to treat fungal infections)
    - fluoxetine, fluvoxamine (used to treat depressive disorders)
    - ticlopidine (used to prevent stroke)
- WELIREG® may affect the way other medicines work, like:
    - hormonal birth control such as desogestrel, ethinylestradiol and levonorgestrel
    - medicines used for sedation and to help sleep such as midazolam

How to take WELIREG®:

- Take WELIREG® exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take WELIREG® with or without food.
- Swallow each tablet whole. Do not break it up.

Usual dose:

- **Adults:** 120 mg (three 40 mg tablets) once per day.
- Your healthcare professional may lower your dose, stop your treatment for a period of time or recommend that you stop treatment completely. This may happen if:
    - you experience serious side effects, or
    - your disease gets worse

Overdose:

If you think you, or a person you are caring for, have taken too much WELIREG®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- If you miss a dose of WELIREG®, take the missed dose as soon as possible on the same day. Take your regular dose of WELIREG® the next day.
- If you vomit after taking WELIREG®, do not take another WELIREG® tablet. Take your regular dose of WELIREG® the next day.
- Do not take 2 doses at the same time.

What are possible side effects from using WELIREG®?

These are not all the possible side effects you may have when taking WELIREG®. If you experience any side effects not listed here, tell your healthcare professional.

- feeling like you're going to throw up (nausea)
- dizziness
- shortness of breath
- feeling tired
- headaches
- muscle pain
- back pain
- stiff joints
- constipation
- changes in weight
- difficulty sleeping
- anxiety
- cough
- chest pain

WELIREG® can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment. These will tell your healthcare professional how WELIREG® is affecting your blood.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness / tiredness, dizziness		X	
COMMON			
Hypoxia (low oxygen in your body): trouble breathing, shortness of breath, chest pain, dizziness, headaches, weakness of limbs, ringing/buzzing/clicking/		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
hissing in ears			
Eye problems: blurred vision, loss of vision in eye, decreased sharpness of vision, blocked eye veins, increased sensitivity of the eyes to light, eye pain or redness, floaters in field vision, eye irritation, swelling and itching of the eyelids		X	
LESS COMMON			
Blood clot (blocked artery): weakness, drooping of face, numbness			X
Intracranial hemorrhage (bleeding within the skull): sudden tingling, weakness, numbness in face, arm, or leg			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store WELIREG® at room temperature (15°C to 30°C).
- Keep out of reach and sight of children.

If you want more information about WELIREG®:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website:

https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.merck.ca, or by calling 1 800 567-2594.

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