1. NAME OF THE MEDICINAL PRODUCT

Welireg® 40 mg film-coated tablets

Patient Alert Card
The marketing of WELIREG is subject to a risk management plan (RMP) including a 'Patient Alert Card'. The 'Patient Alert Card', emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg of belzutifan.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)
Blue, oval shaped, film-coated tablet debossed with '177' on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Welireg is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable or undesirable.

4.2 Posology and method of administration

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Posology
The recommended dose of Welireg is 120 mg (three 40 mg tablets) administered orally once daily, with or without food. Tablets should be swallowed whole.

Treatment should continue until disease progression or unacceptable toxicity occurs.

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 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.

Dose Modifications
Dosage modifications for Welireg for adverse reactions are summarised in Table 1 (see section 4.4).

Table 1: Recommended Dose Modifications

Adverse Reactions	Severity*	Dose Modification
Anaemia *(see section 4.4)*	Grade 3: Haemoglobin (Hgb < 8g /dL) transfusion indicated	• Withhold until resolved to ≤ Grade 2 (Hb ≥ 8 g/dL). • Resume at a reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of anaemia.
	Grade 4: Life-threatening or urgent intervention indicated	• Withhold until resolved to ≤ Grade 2 (Hb ≥ 8 g/dL). • Resume at a reduced dose (reduce by 40 mg) or permanently discontinue.
Hypoxia *(see section 4.4)*	Grade 2: Decreased oxygen saturation with exercise (e.g. pulse oximeter < 88%) intermittent supplemental oxygen	• Consider withholding until resolved • Resume at the same dose or at a reduced dose depending on the severity of hypoxia.
	Grade 3: Decreased oxygen saturation at rest (e.g. pulse oximeter <88% or PaO^2 <=55 mm Hg)	• Withhold until resolved to ≤ Grade 2 • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia.
	Grade 4: Life-threatening	• Permanently discontinue.
Other Adverse Reactions *(see section 4.8)*	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.

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

Special Populations

Elderly (≥ 65 years old)
No dose adjustment is recommended for elderly patients. There are limited data available on the use of Welireg in patients aged 65 years and over (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment of Welireg is recommended in patients with mild or moderate renal impairment (eGFR ≥ 30 mL/minute/1.73 m^2). Welireg has not been studied in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment of Welireg is recommended in patients with mild hepatic impairment. Welireg has not been studied in patients with moderate or severe hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of Welireg in children less than 18 years of age has not yet been established. No data are available.

Method of administration
Welireg is for oral use.
It should be swallowed whole and may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Anaemia due to decreased erythropoietin
Anaemia occurred very commonly in patients receiving Welireg (see section 4.8). Patients should be monitored for anaemia before initiation of and periodically throughout treatment with belzutifan with more frequent monitoring within the first 6 months of treatment (see section 5.1). For patients who develop Grade 3 anaemia (Hb < 8 g/dL), belzutifan should be withheld and patients should be treated according to standard medical practice, including ESA administration until resolved to ⩽ Grade 2 (Hb ⩾ 8 g/dL). For recurrent Grade 3 anaemia, belzutifan should be discontinued. For patients who develop Grade 4 anaemia, the dose of belzutifan should be reduced or permanently discontinued (see section 4.2).

Hypoxia
Belzutifan can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalisation (see section 4.2).

Patients should be monitored for oxygen saturation with pulse oximetry before initiation of and periodically throughout treatment with belzutifan with more frequent monitoring within the first 6 months of treatment (see section 5.1). In light of the risk of hypoxia, smoking cessation is recommended.

For Grade 2 hypoxia, providing supplemental oxygen and continuing or withholding treatment should be considered. If withheld, belzutifan should be resumed at a reduced dose. For patients who have Grade 3 hypoxia, belzutifan should be withheld, hypoxia treated, and dose reduction should be considered. If Grade 3 hypoxia continues to recur, treatment should be discontinued. For Grade 4 hypoxia, treatment should be permanently discontinued (see section 4.2). Patients treated with belzutifan must be given the patient alert card.

Embryo-foetal toxicity
Based on findings in animals, belzutifan may cause foetal harm, including foetal loss, in humans. In a rat study, belzutifan caused embryo-foetal toxicity when administered during the period of organogenesis at maternal exposures that were lower than the human exposures at the recommended dose of 120 mg daily (see section 5.3).

Females of reproductive potential should be advised to use highly effective non-hormonal contraceptive methods during treatment with belzutifan and for 1 week after the last dose, since belzutifan can render some hormonal contraceptives ineffective (see sections 4.5 and 4.6). Advise male patients and their female partners of reproductive potential to use highly effective contraception during treatment with belzutifan and for 1 week after the last dose (see section 4.6). Advise male patients with female partners who are pregnant to use a barrier method of contraception during treatment with belzutifan and 1 week after the last dose.

Information about some of the ingredients
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro and pharmacogenomic studies indicate that belzutifan is metabolised by UGT2B17 and by CYP2C19.

Effects of belzutifan on other medicinal products

Coadministration of Welireg with CYP3A4 substrates, including hormonal contraceptives, decreases concentrations of CYP3A substrates (see sections 5.1 and 5.2), which may reduce the efficacy of these substrates. The magnitude of this reduction may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolisers (see section 5.1).

Avoid coadministration of belzutifan with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its summary of product characteristics.

Coadministration of WELIREG with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding.

Effects of other medicinal products on belzutifan
Co-administration of belzutifan with inhibitors of UGT2B17 or CYP2C19 increases plasma exposures of belzutifan, which may increase the incidence and severity of adverse reactions of belzutifan. Monitor for anaemia and hypoxia and reduce the dosage of belzutifan as recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of belzutifan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Belzutifan is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding
It is unknown whether belzutifan or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with belzutifan and for 1 week after the last dose.

Women of child-bearing potential/ contraception in males and females
Pregnancy Testing
The pregnancy status of females of reproductive potential should be verified prior to initiating treatment with belzutifan.

Contraception
Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman (see sections 4.4 and 5.3).

Females
Females of reproductive potential should be advised to use highly effective contraception during treatment with belzutifan and for at least 1 week after the last dose. Use of belzutifan may reduce the efficacy of hormonal contraceptives. Patients using hormonal contraceptives should be advised to use an alternative non-hormonal contraceptive method or have their male partner use a condom during treatment with belzutifan (see section 4.4).

Males
Male patients and their female partner of reproductive potential should be advised to use highly effective contraception during male patient treatment with belzutifan and for at least 1 week after the

last dose (see section 4.4). Advise male patients with female partners who are pregnant to use barrier method of contraception during treatment with belzutifan and 1 week after the last dose.

Fertility
Based on findings in animals, belzutifan may impair fertility in males and females of reproductive potential (see section 5.3). Advise patients of this potential risk. The reversibility of the effect on fertility is unknown. Family planning should be discussed with patients as appropriate.

4.7 Effects on ability to drive and use machines

Belzutifan may have a minor influence on the ability to drive and use machines. Dizziness and fatigue may occur following administration of belzutifan (see section 4.8).

Patients should be advised not to drive and use machines, until they are reasonably certain belzutifan therapy does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

The safety of belzutifan was evaluated in an open-label Phase 2 clinical study (Study-004), in 61 patients with VHL disease-associated RCC and who did not require immediate nephrectomy or partial nephrectomy. Patients were treated with 120 mg belzutifan once daily. The median duration of exposure to belzutifan was 28.9 months (range: 1.9 to 37.5).

The most common adverse reactions with belzutifan were anaemia (90%), fatigue (71%), dizziness (44%) and nausea (36%).

The most common Grade 3 or 4 adverse reactions were anaemia (10%), and fatigue (5%).

Serious adverse reactions occurred in 5% of patients who received belzutifan, including anaemia, dyspnoea and hypoxia (1 patient each).

Dose interruption of belzutifan due to adverse reactions occurred in about 23% of patients. The most common adverse reactions resulting in dose interruption of belzutifan were fatigue (13.1%), nausea (8.2%), and anaemia (4.9%).
Dose reduction of belzutifan due to adverse reactions occurred in about 11.5% of patients. The adverse reactions resulting in dose reduction of belzutifan were fatigue (8.2%), anaemia, and hypoxia (one patient each 1.6%).

Tabulated list of adverse reactions.
Adverse reactions reported in clinical studies of belzutifan are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Table 2: Adverse drug reactions for Welireg 120 mg Once Daily

Adverse Drug Reaction	**All Grades**	**Grade 3 – 4**
Blood and lymphatic disorders		
Anaemia	Very common	Common
Nervous system disorders		
Dizziness	Very common	Very rare

Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Very common	Common
Hypoxia	Common	Common
Gastrointestinal disorders		
Nausea	Very common	Very rare
General disorders and administration site disorders		
Fatigue	Very common	Common
Investigations		
Weight Increased	Very common	Common

The safety of belzutifan was also evaluated in a Phase 1 clinical study (Study-001), in 58 patients with non-VHL disease-associated advanced solid tumours, treated with belzutifan 120 mg once daily. Study-001 patients differed from VHL-associated RCC patients (Study-004). Study-001 patients were older (median: 62.5 years old; range: 39 to 75 vs. 41.0; range: 19 to 66), had worse ECOG PS (scale 1: 63.8% in study-001 vs. 16.4% in study-004), had metastatic disease, had prior systemic therapies, had more comorbidities, and had lower baseline haemoglobin levels at treatment initiation (median: 119; range: 89 to 173 vs. 140; range 91 to 171). Study-001 had a median duration of exposure to belzutifan of 25.4 weeks (range: 1.1 to 145.9 weeks). The adverse reactions with belzutifan in Study-001 were anaemia (76%), fatigue (71%), dyspnoea (47%), nausea (35%), hypoxia (29%), dizziness (22%) and weight increased (10%). The adverse reactions resulting in dose interruption of belzutifan were hypoxia (10.3%), anaemia (8.6%), dyspnoea (5.2%), fatigue (1.7%) and nausea (1.7%). The adverse reactions resulting in dose reduction of belzutifan were hypoxia (3.4%), nausea (1.7%) and fatigue (1.7%). The adverse reactions resulting in discontinuation were hypoxia (3.4%) and fatigue (1.7%).

Description of selected adverse reactions

Anaemia due to decreased erythropoietin (see section 5.1)
In Study-004 anaemia was reported in 90.2% of all patients with Grade 3 anaemia occurring in 9.8%. Median time to onset of all Grade anaemia events was 30 days (range: 1 day to 8.38 months). Most of the anaemia occurred in the first 3 months of treatment initiation and was not progressive. Three (4.9%) participants had anaemia events leading to study drug interruption and 1 participant (1.6%) had a dose reduction due to anaemia. No participant discontinued treatment due to anaemia. Of the 13 patients that were treated with an ESA, 4 received treatment with both an ESA and blood transfusions, while 9 received treatment with an ESA alone. Patients received an ESA based on haemoglobin levels and physician discretion. Anaemia was reported as resolved in 13 (21.3%) of participants and resolving or not yet resolved in 40 (65.6%) participants.

In another clinical study (Study-001) for the treatment of non-VHL disease-associated advanced solid tumours using the same dose of belzutifan, anaemia was reported in 44 patients (75.9%) with Grade 3 anaemia occurring in 16 patients (27.6%).

Hypoxia (see section 5.2)
In Study-004 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 once daily with no recurrence of hypoxia. In another clinical study (Study-001) for the treatment of non-VHL disease-associated advanced solid tumours using the same dose of belzutifan, hypoxia occurred in 17 patients (29.3%), with Grade 3 hypoxia occurring in 9 patients (15.5%).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulations by using an online form: https://sideeffects.health.gov.il

4.9 Overdose

There is no specific treatment for belzutifan overdose. In cases of suspected overdose, withhold belzutifan and institute supportive care. The highest dose of belzutifan studied clinically was 240 mg daily (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 except for Grade 3 hypoxia observed at 120 mg twice a day and Grade 4 thrombocytopenia observed at 240 mg once daily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, ATC code: L01XX74.

Mechanism of action
Belzutifan is an inhibitor of hypoxia-inducible factor 2 alpha (HIF-2α). HIF-2α is 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-1b) to form a transcriptional complex that regulates expression of downstream genes, including genes associated with cellular proliferation, angiogenesis, and tumour growth (including CCND1, VEGFA, SLC2A1 (GLUT1), IGFBP3, TGFa, AXL, CXCR4, IL6). Belzutifan binds to HIF-2α, and in conditions of hypoxia or impairment of VHL protein function, belzutifan blocks the HIF-2α-HIF-1b interaction, leading to reduced transcription and expression of HIF-2α target genes. *In vivo*, belzutifan demonstrated anti-tumour activity in mouse xenograft models of renal cell carcinoma.

Pharmacodynamic effects
The pharmacodynamic effects of belzutifan were evaluated in patients with VHL disease-associated RCC (Study-004) and in patients with non-VHL disease-associated advanced solid tumours (Study-001). Circulating plasma levels of EPO were monitored in patients as a pharmacodynamic marker of HIF-2α inhibition. Treatment with belzutifan resulted in reductions in EPO at all dose levels. Reductions in EPO were observed to be dose/exposure dependent and showed a plateauing effect on reduction at exposures achieved with doses above 120 mg once daily. In patients with VHL disease-associated RCC receiving 120 mg once daily of belzutifan, peak EPO suppression occurred at 2 weeks of treatment (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

Pharmacogenomics
Belzutifan is primarily metabolised by UGT2B17 and CYP2C19. The activity of these enzymes varies among individuals who carry different genetic variants, which may impact belzutifan concentrations. Poor metabolisers are individuals who are considered to have no enzyme activity. Approximately 15% of Caucasians, 11% of Latinos, 6% of African Americans, 38% of South Asians, and 70% of East Asians are UGT2B17 poor metabolisers. Approximately 2% of Caucasians, 1% of Latinos, 5% of African Americans, 8% of South Asians, and 13% of East Asians are CYP2C19 poor metabolisers. Approximately 0.3% of Caucasians, 0.1% of Latinos, 0.3% of African Americans, 3% of South Asians, and 9% of East Asians are dual UGT2B17 and CYP2C19 poor metabolisers.

The impact of CYP2C19 and UGT2B17 poor metabolisers on belzutifan exposure was assessed in a population PK analysis. Based on the analysis, VHL disease-associated RCC patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolisers, are projected to have 1.5-, 1.6- or 2.3-fold the exposures (steady-state AUC_{0-24}), respectively, compared to a typical reference patient (UGT2B17 intermediate metaboliser, CYP2C19 non-poor metaboliser) for the recommended dose. No dose adjustment is recommended based on exposure-response analyses for efficacy and safety and the risk-benefit profile.

Clinical efficacy

The efficacy of belzutifan was investigated in Study-004, an open-label Phase 2 clinical study in 61 patients with confirmed VHL disease, based on a VHL germline alteration, who had at least one measurable solid tumour (as defined by RECIST v1.1) localised to the kidney and who did not require immediate surgery. Enrolled patients had other VHL-associated tumours including CNS haemangioblastomas and pNET, identified by radiological appearance. The study excluded patients who had any evidence of metastatic disease, either RCC or other VHL disease-associated tumours. Other exclusion criteria were immediate need for surgical intervention for tumour treatment, any major surgical procedure completed within 4 weeks prior to study enrolment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease-associated RCC. Patients were monitored for anaemia and hypoxia before initiation of belzutifan, and then every 2 weeks for the first month, monthly for the next 5 months, and then every 3 months thereafter throughout treatment.

The study population characteristics were: median age of 41 years [range 19-66 years], 3.3% age 65 or older; 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 encompassing ablative procedures, partial nephrectomy, radical nephrectomy.
The median diameter of RCC target lesions per central independent review committee (IRC) was 2.2 cm (range 1-6.1). Median time from initial radiographic diagnosis of VHL-associated RCC tumours that led to enrolment on Study 004 to the time of treatment with WELIREG was 17.9 months (range 2.8-96.7).

Patients received belzutifan 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 effect of intermittent use and long treatment interruptions of belzutifan have not been evaluated.

The primary efficacy endpoint for the treatment of VHL disease-associated RCC was overall response rate (ORR) measured by radiology assessment using RECIST v1.1 as assessed by IRC. Secondary efficacy endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), time to response (TTR), and time to surgery (TTS).
Table 3 summarises the efficacy results for VHL disease-associated RCC tumours in Study-004 at a median follow-up time of 29.2 months (range 4.2-37.5). The median duration of exposure was 28.9 months (range 1.9-37.5).

Table 3: Efficacy results in VHL disease-associated RCC tumours in Study-004

Endpoint	**Belzutifan 120 mg daily n=61**
Overall response rate	
ORR* (95% CI)	59.0% (45.7, 71.4)
Complete response	3.3%
Partial response	55.7%
Stable disease	39.3%

Disease control rate†	98.4%
Response duration‡	
Median in weeks (range)	Not reached (36.1+, 119.9+)
% (n) with duration ≥ 18 months	95.0% (19)
Time to response	
Median in weeks (range)	47.6 (11.6, 96.6)
Time to surgery	
Median in weeks (95% CI)	Not reached (NE, NE)
PFS‡	
Median in weeks (95% CI)	Median not estimated§
24-month PFS rate	94.6%

* Response: Best objective response as confirmed complete response or partial response
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates
§ Reliable median could not be estimated due to the number of progression events (n=7) and a progression event that occurred at the latest timepoint when only 1 patient was at risk.
NE = Not estimable

During this period of treatment, two out of 61 (3.3%) patients required an RCC tumour reduction procedure. For comparison, in one retrospective natural history study of VHL patients with RCC, 28.7% of patients had their first tumour reduction procedure within 24 months of follow-up.

Objective response rates were in other VHL diseases associated tumours: 38% CNS haemangioblastomas (95% CI: 24.7, 52.8; 19 out of 50 patients), and 90% for pancreatic neuroendocrine tumours (95% CI: 68.3, 98.8; 18 out of 20 patients).

5.2 Pharmacokinetic properties

The pharmacokinetics of belzutifan are similar in healthy subjects and patients with solid tumours including advanced RCC. Based on a population-PK model analysis, the steady-state geometric mean (GCV%) for C_{max} and $AUC_{0\text{-}24hr}$ for 120 mg once daily in patients with VHL disease-associated RCC are predicted to be 1.4 µg/mL (39.8%) and 16.7 µg•hr/mL (52.3%), respectively. Steady-state is reached after approximately 3 days of once daily dosing with belzutifan.

Absorption
Following single-dose oral administration of 120 mg of belzutifan, peak plasma concentrations (median T_{max}) of belzutifan occurred at 1.5 hours post dose.

Effect of food
A high-fat, high-calorie meal delayed peak belzutifan concentration by approximately 2 hours, but had no effect on exposure (AUC). There was a modest decrease of C_{max} by 35% following consumption of a high-fat, high-calorie meal, but this was not clinically meaningful. Therefore, belzutifan can be taken without regard to food.

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

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

Metabolism

Belzutifan is primarily metabolised by UGT2B17 and CYP2C19 and to a lesser extent by CYP3A4. Both UGT2B17 and CYP2C19 display genetic polymorphisms (see section 5.1).

Linearity
The plasma C_{max} and AUC increased in a dose-proportional manner following doses up to the recommended dose for belzutifan.

Special Populations

Renal impairment
No relevant increase in exposure (AUC) was observed for subjects with mild or moderate renal impairment. Renal impairment (as evaluated by eGFR) was not identified as a significant covariate in the population pharmacokinetic analysis. The pharmacokinetics of belzutifan have not been studied in patients with severe renal impairment (see sections 4.2 and 5.2).

Hepatic impairment
No relevant increase in exposure (AUC) was observed for subjects with mild hepatic impairment (using NCI index) based on population pharmacokinetic analysis. The pharmacokinetics of belzutifan have not been studied in patients with moderate or severe hepatic impairment (see sections 4.2 and 5.2).

Dual UGT2BI7 and CYP2C19 Poor Metabolisers
Patients who are dual UGT2B17 and CYP2C19 poor metabolisers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of belzutifan and should be closely monitored (see sections 4.4, 4.8 and 5.1).

Effects of Age, Gender, Ethnicity, Race, and Body Weight
Based on a population pharmacokinetic analysis, age, gender, ethnicity, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of belzutifan. Potential differences in exposure across races are possible due to different frequencies of metabolising enzymes (see section 5.1).

Paediatric population
No studies with belzutifan have been performed in paediatric patients.

5.3 Preclinical safety data

Carcinogenicity
Carcinogenicity studies have not been conducted with belzutifan.

Genotoxicity
Belzutifan was not genotoxic in *in vitro* bacterial mutagenesis and micronucleus assays, and an *in vivo* rat micronucleus assay.

Reproductive toxicity
Fertility studies with belzutifan have not been conducted. In the 3-month repeat-dose toxicity study in rats, irreversible testicular atrophy/degeneration was observed at exposures lower than the human exposure at the recommended dose of 120 mg daily. There were no findings in female reproductive organs in either rat or dog 3-month toxicity studies.

Development
In a rat embryo-foetal development study, administration of belzutifan during organogenesis caused embryo-foetal lethality up to 100%, reduced foetal body weight, and foetal skeletal abnormalities at exposures similar to or below the human exposure at the recommended dose of 120 mg daily. Based

on the observed embryo-foetal lethality in rats treated with belzutifan, a pre- and postnatal developmental toxicity study was not conducted.

Acute toxicity
No formal acute toxicity studies have been conducted. However, the toxicity after a single-dose was assessed from the repeat-dose oral toxicity studies in rats (from 2 to 200 mg/kg/day) and dogs (from 1 to 30 mg/kg/day). No acute toxicities were observed in these studies

Chronic toxicology
Repeat-dose oral toxicity studies were conducted in rats and dogs for up to 3 months duration. Reversible decreases in red blood cell parameters were observed in rats and dogs at exposures lower than the human exposure at the recommended dose of 120 mg daily. Belzutifan caused irreversible testicular atrophy/degeneration and oligospermia in rats at exposures lower than the human exposure at the recommended dose of 120 mg daily. No testicular toxicity was observed in dogs up to an exposure similar to the human exposure at the recommended dose of 120 mg daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet
Cellulose Microcrystalline
Mannitol
Hypromellose Acetate Succinate
Crosscarmellose Sodium
Magnesium Stearate
Silica, Colloidal Anhydrous

Film-coating
Polyvinyl Alcohol (Part hydrolyzed)
Titanium Dioxide
Macrogol (Macrogol 3350)
Talc
Indigo Carmine Aluminum Lake

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
It is recommended to keep at room temperature.

6.5 Nature and contents of container

Each carton contains a high density polyethylene (HDPE) bottle with a polypropylene child-resistant closure with two silica gel desiccants. Each bottle contains 90 film-coated tablets.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND IMPORTER

Merck Sharp & Dohme (Israel-1996) Company Ltd., 34 Ha'charash St., Hod Hasharon.

8. REGISTRATION NUMBER

173-89-37469

Revised in October 2025.