NEW ZEALAND DATA SHEET

1. PRODUCT NAME

WELIREG® 40 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

WELIREG (belzutifan) is supplied as 40 mg film-coated tablets for oral administration.

Excipients with known effect:

Each WELIREG film-coated tablet contain 40 mg of belzutifan.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

WELIREG 40 mg tablet is a blue, oval shaped, film-coated tablet with a length of 13.36 mm and a width of 8.20 mm, with “177” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

von Hippel-Lindau (VHL) disease associated tumours

WELIREG (belzutifan) is indicated for the treatment of adult patients with von-Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), not requiring immediate surgery.

Advanced Renal Cell Carcinoma (RCC)

WELIREG (belzutifan) is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and antiangiogenic therapies.

4.2 Dose and method of administration

Recommended Dosing

The recommended dose of WELIREG is 120 mg (three 40 mg tablets) administered orally once daily, with or without food. Swallow tablets whole.

If a dose of WELIREG is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for WELIREG the next day. Extra tablets should not be taken to make up for the missed dose. If vomiting occurs any time after taking WELIREG, do not retake the dose. The next dose should be taken the next day. Treatment should continue until disease progression or unacceptable toxicity occurs.

Dose Modifications

Dosage modifications for WELIREG for adverse reactions are summarised in Table 1.

Table 1: Recommended Dose Modifications

Adverse Reactions	Severity*	Dose Modification
Anaemia due to decreased erythropoietin *[see Section 4.4 Special Warnings and Precautions for Use]*	Grade 3	• Withhold until resolved to ≤ Grade 2. • Resume at the same or reduced dose (reduce by 40 mg); consider discontinuing depending on the severity and persistence of anaemia.
	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 Section 4.4 Special Warnings and Precautions for Use]*	Grade 3 (asymptomatic)	• Option to continue or 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 3 (symptomatic)	• 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	• Permanently discontinue.
Other Adverse Reactions *[see Section 4.8 Undesirable Effects]*	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 Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

Special Populations

Paediatric Patients

The safety and efficacy of WELIREG have not been established in paediatric patients less than 18 years of age [see *Section 5.2 Pharmacokinetic Properties*].

Elderly Patients

No dose adjustment of WELIREG is recommended in elderly patients [See *Section 5.2 Pharmacokinetic Properties*].

Patients with Renal Impairment

No dose adjustment of WELIREG is recommended in patients with mild and moderate renal impairment. WELIREG has not been studied in patients with severe renal impairment [See *Section 5.2 Pharmacokinetic Properties*].

Patients with 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 Pharmacokinetic Properties*].

4.3 Contraindications

None.

4.4 Special warnings and precautions for use

Anaemia due to Decreased Erythropoietin

In a clinical trial (LITESPARK-004) with WELIREG for the treatment of patients with VHL disease-associated RCC, anaemia was reported in 55 patients (90.2%). Grade 3 anaemia occurred in 7 patients (11.5%) [See *Section 4.8. Undesirable Effects*]. Median time to onset of all Grade anaemia 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. The median number of ESA doses administered to patients was 5 (range 1-35). Patients received an ESA based on haemoglobin levels and physician discretion [See *Section 5.1 Pharmacodynamic Properties*]. In LITESPARK-005, a clinical trial with WELIREG for the treatment of patients with advanced RCC, anaemia occurred in 83% of patients, 119 patients (32%) had Grade 3 and 2 patients (0.5%) had Grade 4 anaemia [See *Section 4.8. Undesirable Effects*]. Median time to onset of anaemia was 29 days (range: 1 day to 27 months). Of the patients with anaemia, 67 patients (22%) received transfusions only, 62 patients (20%) of patients received ESAs only and 42 patients (14%) received both transfusion and ESAs. The median number of ESA doses administered to patients was 6.5 (range: 1-87). Patients received an ESA based on haemoglobin levels and physician discretion. In another clinical trial (Study-001) for the treatment of non-VHL disease-associated advanced solid tumours using the same dose of WELIREG, anaemia was reported in 44 patients (75.9%). Grade 3 anaemia occurred in 16 patients (27.6%).

Monitor for anaemia before initiation of and periodically throughout treatment with WELIREG. For patients who develop Grade 3 anaemia, withhold WELIREG and treat according to standard medical practice, including erythropoiesis-stimulating agent (ESA) administration and/or transfusion until resolved to ≤ Grade 2; then resume at the same or reduced dose. For recurrent Grade 3 anaemia, consider discontinuing WELIREG.

For patients who develop Grade 4 anaemia, withhold WELIREG; then resume at a reduced dose or permanently discontinue for recurrent Grade 4 anaemia [See *Section 4.2 Dose and Method of Administration*].

Hypoxia

In a clinical trial (LITESPARK-004) with WELIREG for the treatment of patients with VHL disease-associated RCC, Grade 3 hypoxia occurred in 1 patient (1.6%) [See *Section 4.8. Undesirable Effects*]. In LITESPARK-005, a clinical trial with WELIREG for the treatment of patients with advanced RCC, hypoxia occurred in 15% of patients and 38 patients (10%) had Grade 3 hypoxia and 1 patient (0.3%) had Grade 4 hypoxia [See *Section 4.8. Undesirable Effects*]. Of the patients with hypoxia, 70% were treated with oxygen therapy. Median time to onset of hypoxia was 1 month (range: 1 day to 21 months).

In another clinical trial (Study-001) for the treatment of non-VHL disease-associated advanced solid tumours 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 periodically throughout treatment with WELIREG. For Grade 3 asymptomatic hypoxia, consider providing supplemental oxygen and consider continuing or withholding treatment. If withheld, resume at a reduced dose. For patients who have Grade 3 symptomatic hypoxia, withhold WELIREG, treat hypoxia, and consider dose reduction. If symptomatic hypoxia continues to recur, discontinue treatment. For Grade 4 hypoxia, permanently discontinue treatment [See *Section 4.2 Dose and Method of Administration*].

Embryo-fetal Toxicity

Based on findings in animals, WELIREG may cause fetal harm, including fetal loss, in humans. In a rat study, WELIREG caused embryo-fetal 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. Advise females of reproductive potential to use highly effective contraceptive methods during treatment with WELIREG and for 1 week after the last dose due to the potential risk to the fetus. Advise males with female partners of reproductive potential to use highly effective contraception during treatment with WELIREG and for 1 week after the last dose [S*ee Section 4.6 Fertility, pregnancy and lactation* and *Section 5.3 Preclinical safety data*].

4.5 Interaction with other medicines and other forms of interaction

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

Effects of WELIREG on Other Drugs

Coadministration of WELIREG with CYP3A4 substrates, including hormonal contraceptives, decreases concentrations of CYP3A4 substrates, which may reduce the efficacy of these substrates. The magnitude of this decrease may be more pronounced in patients who are dual UGT2B17 and CYP2C19 poor metabolisers [*See Section 5.1 Pharmacodynamic properties* and *Section 5.2 Pharmacokinetic properties*].

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

Effects of Other Drugs on WELIREG

Co-administration with inhibitors of UGT2B17 or CYP2C19 is expected to increase plasma belzutifan exposure. Dose adjustment is not required on co-administration with inhibitors of UGT2B17 or CYP2C19. Drugs that induce CYP2C19 are expected to reduce plasma exposures of WELIREG.

In patients with reduced activity of both UGT2B17 and CYP2C19, coadministration of WELIREG with CYP3A4 inhibitors is expected to increase the plasma exposure of belzutifan, which may increase the risk of adverse reactions of WELIREG. Monitor for anaemia and hypoxia and reduce the dosage of WELIREG as recommended [See *Section 4.2. Dose and Method of Administration, Dose Modifications*].

4.6 Fertility, pregnancy and lactation

Pregnancy

Based on findings in animal studies, WELIREG may cause fetal harm, including fetal loss, when administered to a pregnant woman. There are no available data on the use of WELIREG in pregnant women to evaluate drug-associated risk. In a rat embryo-fetal development study, administration of WELIREG during organogenesis caused embryo-fetal lethality, reduced fetal body weight, and fetal skeletal abnormalities at exposures similar to or below the human exposure at the recommended dose of 120 mg daily. Advise females of reproductive potential of the potential risk to a fetus.

Lactation

There are no data on the presence of WELIREG or its metabolites in human milk, their effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with WELIREG and for 1 week after the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating treatment with WELIREG.

Contraception

WELIREG may cause embryo-fetal harm, including fetal loss, when administered to a pregnant woman [See *Section 4.6 Fertility, pregnancy* and *lactation]*.

Females

Females of reproductive potential should be advised to use highly effective contraception during treatment with WELIREG and for at least 1 week after last dose. Use of WELIREG 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 WELIREG [See *Section 4.5 Interaction with other medicines* and *other forms of interactions*].

Males

Advise male patients with female partners of reproductive potential to use highly effective contraception during treatment with WELIREG and for at least 1 week after the last dose.

Infertility

Based on findings in animals, WELIREG may impair fertility in males and females of reproductive potential [See *Section 5.3 Preclinical Safety Data, Reproduction*]. Advise patients of this potential risk. The reversibility of the effect on fertility is unknown.

4.7 Effects on ability to drive and use machines

Dizziness and fatigue may occur following administration of belzutifan [See *Section 4.8 Undesirable Effects*].

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

Von Hippel-Lindau (VHL) disease associated tumours

Summary of the Safety Profile

The safety of belzutifan was evaluated in an open-label Phase 2 clinical study (LITESPARK-004), in 61 patients with VHL disease-associated RCC and who did not require immediate surgery. Patients were treated with 120 mg belzutifan once daily. The median duration of exposure to belzutifan was 37.3 months (range 1.9 to 46.1 months).

The most common adverse reactions under treatment with belzutifan were anaemia (90%), fatigue (74%), dizziness (46%), and nausea (39%), and dyspnoea (26%).

The most common adverse reactions resulting in dose interruption of belzutifan were fatigue (11.5%), nausea (9.8%), dizziness (4.9%), and anaemia (3.3%). The most common adverse reactions resulting in dose reduction of belzutifan were fatigue (8.2%), anaemia (3.3%) and hypoxia (1.6%). Belzutifan was discontinued due to adverse reaction in 4 patients.

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies with 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 reactions for WELIREG 120mg Once Daily*

System Organ Class	**Adverse Drug Reaction**
Blood and lymphatic disorders	
Very Common	anaemia
Nervous system disorders	
Very Common	dizziness
Respiratory, thoracic and mediastinal disorders	
Very Common	dyspnoea
Common	hypoxia
Gastrointestinal disorders	
Very Common	nausea
General disorders and administration site disorders	
Very Common	fatigue
Investigations	
Very Common	weight increased

*Adverse reaction frequencies presented in Table 2 may contain contributions from the underlying disease.

Advanced Renal Cell Carcinoma

Summary of the Safety Profile

The safety of belzutifan was evaluated in a Phase 3 clinical study (LITESPARK-005), in 372 patients with advanced RCC. Patients were treated with 120 mg belzutifan once daily. The median duration of exposure to belzutifan was 7.6 months (range 0.1 to 35.8 months).

The most common adverse reactions under treatment with belzutifan were anaemia (83%), fatigue (31%), dyspnoea (15%), hypoxia (15%), nausea (18%) and dizziness (12%).

The most common adverse reactions resulting in dose interruption of belzutifan were anaemia (8.6%), hypoxia (5.6%), fatigue (1.6%), dizziness (1.6%), dyspnoea (1.6%) and nausea (1.3%). The most common adverse reactions resulting in dose reduction of belzutifan were hypoxia (5.6%) and anaemia (3.0%). Belzutifan was discontinued due to adverse reaction in 5.9% of patients.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies of belzutifan are listed in Table 3. These reactions are presented by 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 3: Adverse reaction in patients treated with belzutifan 120mg once daily in adult patients with advanced RCC

System Organ Class	**Adverse reactions**
Blood and lymphatic disorders	
Very common	Anaemia*
Nervous system disorders	
Very common	Dizziness
Respiratory, thoracic and mediastinal disorders	
Very Common	Dyspnoea, hypoxia
Gastrointestinal disorders	
Very Common	Nausea
General disorders and administration site disorders	
Very Common	Fatigue
Investigations	
Common	Weight increased

*Anaemia includes anaemia and haemoglobin decreased

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 (LITESPARK-004). Study-001 patients were older, had worse ECOG PS, had metastatic disease, had prior therapies, had more comorbidities, and had lower baseline haemoglobin levels at treatment initiation. Study-001 had a median duration of exposure to belzutifan of 25.4 weeks (range: 1.1 to 145.9 weeks). The adverse reactions under treatment 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%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

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 600 mg total daily dose (200 mg three times a day). At doses of 320 mg to 600 mg daily in 26 patients, the most common adverse reactions were anaemia (92%), dyspnoea (42%), and fatigue (42%).

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Other antineoplastic agents, 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 stabilisation and accumulation of HIF-2α. Upon stabilisation, 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

Circulating plasma levels of erythropoietin (EPO) were monitored in patients as a pharmacodynamic marker of HIF-2α inhibition. 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. The maximum EPO suppression occurred following 2 weeks of consecutive dosing of WELIREG (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

The incidence of Grade 3 anaemia increased with higher belzutifan exposure in patients with baseline haemoglobin levels <12 g/dL [See *Section 4.4 Special warnings and precautions for use*].

Cardiac Electrophysiology

At the recommended dose (120 mg once daily) for WELIREG, there were no clinically relevant effects on the QTc interval.

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. Expected frequencies in the Japanese population for the UGT2B17, CYP2C19, and dual UGT2B17 and CYP2C19 poor metabolisers are approximately 77%, 19%, and 15%, respectively. Expected frequencies in the United States population for the UGT2B17, CYP2C19, and dual UGT2B17 and CYP2C19 poor metabolisers are approximately 16%, 3%, and 0.5%, respectively based on the reported proportion of the US population represented by major racial/ethnic groups.

The impact of CYP2C19 and UGT2B17 poor metabolisers on belzutifan exposure was assessed in a population PK analysis. Based on the population PK model, patients who are CYP2C19, UGT2B17, or dual UGT2B17 and CYP2C19 poor metabolisers, are projected to have 1.3-, 2.7- or 3.3-fold the exposures (steady-state $AUC_{0\text{-}24hr}$), respectively, compared to a typical reference patient (UGT2B17 extensive metaboliser, CYP2C19 extensive/intermediate 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

Clinical studies in adult patients with von Hippel-Lindau (VHL) disease associated tumours

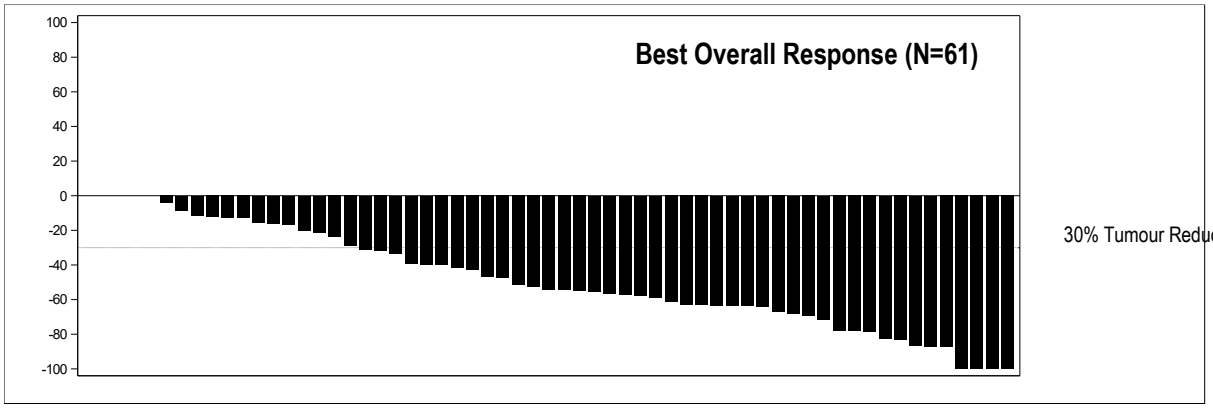
The efficacy of WELIREG was investigated in LITESPARK-004, an open-label Phase 2 clinical trial in 61 patients with VHL disease who had at least one measurable solid tumour (as defined by RECIST v1.1) localised to the kidney and who did not require immediate surgery. Patients received WELIREG at a dose 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 tumours, an immediate need for surgical intervention for tumour 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. Other VHL disease-

associated tumours in patients included pancreatic lesions (100.0%) of which 36.1% were pancreatic neuroendocrine tumours, CNS hemangioblastomas (82.0%), and retinal angiomas (19.7%).

The primary efficacy endpoint for the treatment of VHL disease-associated RCC was objective response rate (ORR) measured by Integrated Radiology and Oncology Assessment (IRO) assessment using RECIST v1.1 as assessed by a central independent review committee (IRC). Additional efficacy endpoints included disease control rate (DCR), response duration, progression-free survival (PFS), time to response (TTR), and time to surgery (TTS). Radiographic endpoints were assessed by IRC using RECIST v1.1. The clinical benefit of WELIREG in reducing RCC tumour size, and slowing the growth of tumours, was supported by pre-treatment and post-treatment linear growth rate of 3.26 and -3.42 mm/year, respectively in LITESPARK-004. A total of 91.8% of participants (56/61) had a decrease in the sum of target tumour diameters (Figure 1). After a median follow-up time of 37.7 months, seven out of 61 (11.5%) patients required an RCC tumour reduction procedure during treatment. In a natural history study of VHL, RCC patients undergoing active surveillance and local therapy, 30% and 57% of patients, respectively had ≥ 1 renal surgery within 2 and 5 years of follow-up. Table 4 summarises the efficacy results for VHL disease-associated RCC tumours in LITESPARK-004.

Figure 1: Waterfall Plot- Percentage Change in Total Sum of RCC Target Lesions Diameters From Baseline to Post-Baseline Maximum % Reduction (RECIST 1.1)- IRC Efficacy Analysis Set – Patients with Evaluable RCC Tumours at Baseline



Subjects without either post-baseline evaluable lesion measurements or target lesions or with all post-baselinenon-evaluable time-point responses appear as blank on the right of the figure. Number (%) of patients with maximum % reduction in sum of diameters of target lesions < 0 = 56 (91.8) Date of Data Cut-off: 01APR2022

Table 4: Efficacy Results for WELIREG for VHL Disease-Associated RCC Tumours

Endpoint	**WELIREG 120 mg daily n=61**
Objective Response Rate	
ORR* % (95% CI)	63.9% (50.6, 75.8)
Complete response	6.6%
Partial response	57.4%
Stable disease	34.4%
Disease Control Rate†	98.4%
Response Duration‡	
Median in months (range)	NE (5.4+, 35.8+)
% (n) with duration ≥ 12 months	100.0% (35)
Time to Response	
Median in months (range)	11.1 (2.7, 30.5)
Time to Surgery	
Median in months (95% CI)	NE (NE, NE)
PFS‡	
Median in months (95% CI)	NE (38.5, NE)
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 and too few patients were at risk at the maximum follow up months
\+ Denotes ongoing response
NE = Not estimable
Data cut-off: April1, 2022

Efficacy endpoints for the treatment of other VHL disease-associated tumours included ORR, DCR and response duration, as assessed by IRC using RECIST v1.1. These results are shown in Table 5.

Table 5: Efficacy Results for WELIREG for Other VHL Disease-Associated RCC Tumours

	WELIREG 120 mg daily n=61		
Endpoint	**Patients with Evaluable Pancreatic Lesions n=61**	**Patients with Evaluable Pancreatic Neuroendocrine Tumours n=22**	**Patients with Evaluable CNS Hemangioblastomas n=50**
Objective Response Rate			
ORR % (95% CI)	83.6% (71.9, 91.8)	90.9% (70.8, 98.9)	44% (30.0, 58.7)
Complete response	27.9%	31.8%	8.0%
Partial response	55.7%	59.1%	36.0%
Stable disease	14.8%	9.1%	46.0%
Disease Control Rate†	98.4%	100.0%	90.0%
Response Duration‡			
Median in weeks (range)	Not reached (2.6+, 37.3+)	Not reached (11.0+, 37.3+)	Not reached (3.7+, 38.7+)
% (n) with duration ≥ 12 months	100.0% (45)	100.0% (12)	90.2% (16)

† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates
\+ Denotes ongoing response
Data cut-off: April 1, 2022

Retinal haemangioblastoma response was determined by IRC assessment of fundoscopic photographs. Seventeen patients were determined by investigators to have baseline retinal haemangioblastomas. Twelve out of these 17 patients were evaluable for response with follow-up evaluations. Responses were measured for each eye separately and confirmed by subsequent evaluations. All 12 patients improved, and all had improvement for greater than 12 months, with 9 patients continuing to improve for greater than 30 months. The median time to response was 2.7 months (range 2.5-8.3 months).

Clinical studies in adult patients with advanced renal cell carcinoma (RCC)

The efficacy of belzutifan was evaluated in LITESPARK-005, an open-label, randomised, active-controlled Phase 3 clinical study comparing belzutifan with everolimus in 746 patients with unresectable, locally advanced or metastatic clear cell RCC that has progressed following PD-1/L1 checkpoint inhibitor and VEGF receptor targeted therapies either in sequence or in combination. Patients could have received up to 3 prior treatment regimens and must have measurable disease per RECIST v1.1. Patients were randomised in a 1:1 ratio to receive 120 mg belzutifan or 10 mg everolimus by oral administration once daily. Randomisation was stratified by International Metastatic RCC Database Consortium (IMDC) risk categories (favourable versus intermediate versus poor) and number of prior VEGF receptor targeted therapies (1 versus 2-3).

Patients were evaluated radiologically at Week 9 from the date of randomisation, then every 8 weeks through Week 49, and every 12 weeks thereafter.

Among the 746 patients in LITESPARK-005, the baseline characteristics were: median age 63 years (range 22-90 years), 42% age 65 or older; 78% male; 79% White; 12% Asian; 1.1% Black or African American; 43% ECOG performance status 0 and 55% ECOG performance status 1. Prior therapies: 13% of patients had 1 prior line of therapy, 43% had 2 prior lines of therapy and 43% had 3 prior lines of therapy; 49% received 2 to 3 prior VEGF receptor targeted therapies. Patient distribution by IMDC risk categories was 22% favourable, 66% intermediate, and 12% poor.

The primary efficacy outcome measures were Progression-Free Survival (PFS) measured by BICR using RECIST v1.1, and Overall Survival (OS). Secondary efficacy outcome measures included objective response rate (ORR), and duration of response (DOR) by BICR using RECIST v1.1.

The trial demonstrated a statistically significant improvement of PFS for patients randomised to WELIREG compared with everolimus. The efficacy results for advanced RCC in LITESPARK-005 are summarised in Table 6.

Table 6: Efficacy Results (BICR assessment) for belzutifan in LITESPARK 005

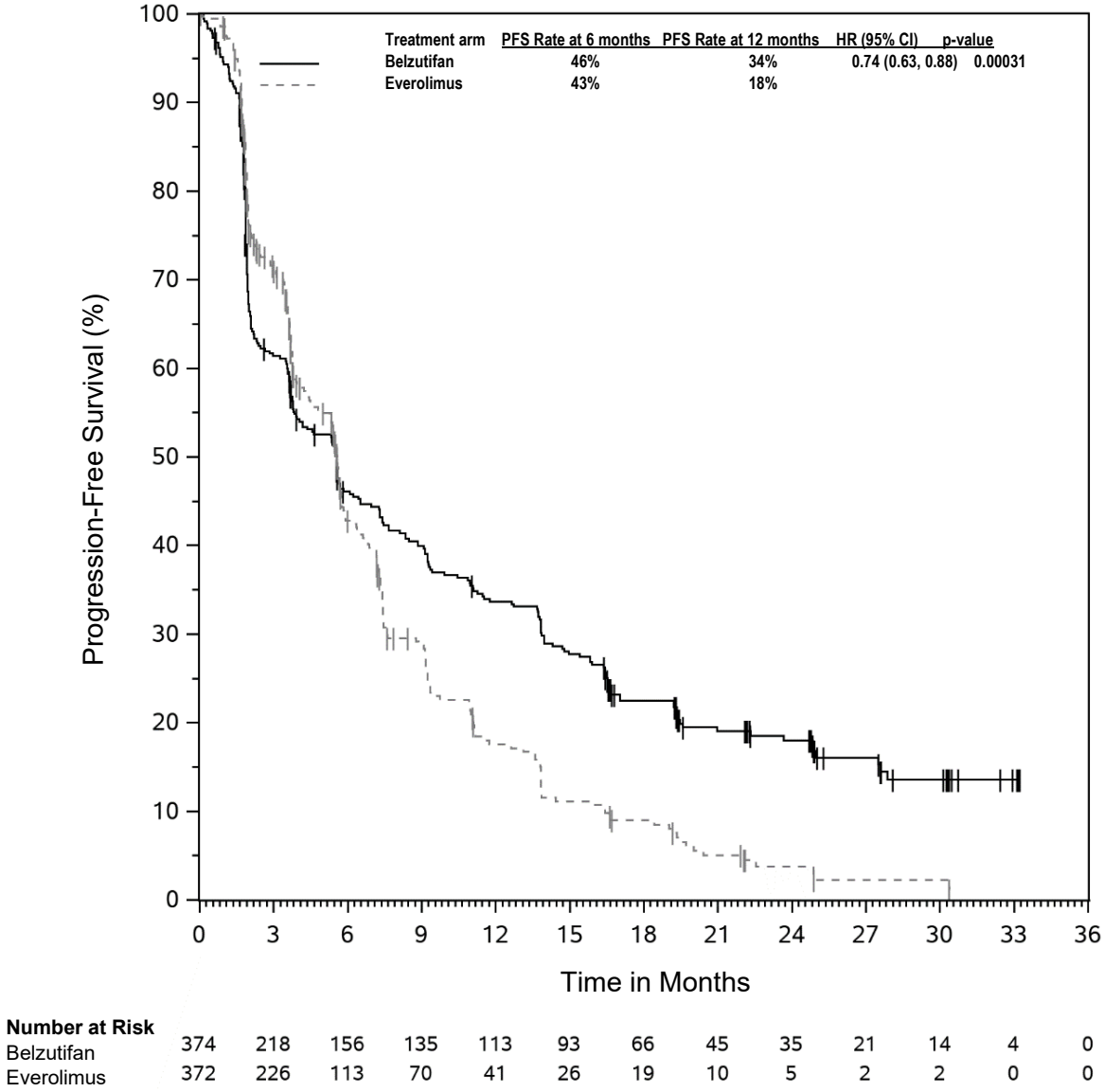
Efficacy Outcome Measure	**Belzutifan n=374**	**Everolimus n=372**
PFS, % (n)*		
Number of events	69% (257)	70% (262)
Progressive disease	63% (234)	60% (222)
Median PFS in months (95% CI)†	5.6 (3.9, 7.0)	5.6 (4.8, 5.8)
Hazard ratio‡ (95% CI)	0.75 (0.63, 0.90)	
p-Value	0.00077	
ORR, % (n) (95% CI)	22% (82) (17.8, 26.5)	3.5% (13) (1.9, 5.9)
Complete response	2.7% (10)	0% (0)
Partial response	19% (72)	3.5% (13)
p-Value	<0.00001	
Duration of Response		
Median in months (range)	NR (1.7+ - 23.2+)	17.2 (3.8 – 18.0+)
% with DoR ≥ 12 months†	74%	68%

* Based on first pre-specified interim analysis.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on the stratified Cox regression model.
+ Indicates there is no progressive disease by the time of last disease assessment.

At a subsequent pre-specified analysis with median follow-up time of 17.8 months (range: 0.2 - 39.1 months) there were 289 PFS events for WELIREG and 276 PFS events for everolimus. The median PFS was 5.6 months (95% CI: 3.8, 6.5) for WELIREG versus 5.6 months (95% CI: 4.8, 5.8) for everolimus. The PFS hazard ratio was 0.74 (95% CI: 0.63, 0.88) (Figure 2). The median duration of response was 19.5 (range: 1.9 - 31.6+) for WELIREG versus 13.7 (range: 3.8 – 21.2+) for everolimus. Based on Kaplan-Meier estimates, patients with a DOR ≥ 12 months was 73% for WELIREG versus 62% for everolimus. At the pre-specified interim analysis, OS favoured belzutifan over everolimus, but did not reach statistical significance. The median OS was 21.4 months (95% CI: 18.2, 24.3) for WELIREG versus 18.1 months (95% CI: 15.8, 21.8) for everolimus resulting in a HR of 0.88 (95% CI: 0.73, 1.07).

The median Time to Response (TTR) was 3.8 months (range: 1.7 - 22.0) in the belzutifan group and 3.7 months (range: 1.8 - 5.4) in the everolimus group. ORR analysis demonstrated ORR of 22.7% for WELIREG versus 3.5% for everolimus.

Figure 2: Kaplan-Meier Curve for Radiographic Progression-free Survival in LITESPARK-005



Number at Risk													
Belzutifan	374	218	156	135	113	93	66	45	35	21	14	4	0
Everolimus	372	226	113	70	41	26	19	10	5	2	2	0	0

5.2 Pharmacokinetic properties

General Introduction

The pharmacokinetics of belzutifan are similar in healthy subjects and patients with solid tumours including advanced RCC. C_{max} and AUC increase proportionally over a dose range of 20 mg to 120 mg. Based on population PK analysis, the simulated geometric mean steady-state (CV%) C_{max} is 1.5 µg/mL (46%) and $AUC_{0\text{-}24hr}$ is 20.8 µg•hr/mL (64%) in patients treated with 120 mg belzutifan. Steady-state is reached after approximately 3 days.

Absorption

Following single-dose oral administration of 120 mg of WELIREG, peak plasma concentrations (median T_{max}) of belzutifan occurred at 1 to 2 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 24% following consumption of a high-fat, high-calorie meal, but this was not clinically meaningful. Therefore, WELIREG can be taken without regard to food.

Distribution

Based on the population PK analysis, the mean (CV%) volume of distribution is 120 L (28.5%). Plasma protein binding of WELIREG is 45%. The blood-to-plasma concentration ratio of WELIREG is 0.88.

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 Pharmacodynamic properties*].

Elimination

Based on the population PK analysis, the mean (CV%) clearance is 5.89 L/hr (60.6%) and the mean elimination half-life is approximately 14 hrs.

Following oral administration of radiolabelled belzutifan to healthy subjects, approximately 49.6% of the dose was excreted in urine and 51.7% in feces (primarily as inactive metabolites). Approximately 6% of the dose was recovered as parent drug in urine.

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 *Section 4.2 Dose and Method of Administration* and *Section 4.4 Special Warnings* and *Precautions for Use*].

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 *Section 4.2 Dose and Method of Administration* and *Section 4.4 Special Warnings* and *Precautions for Use*].

Dual UGT2BI7 and CYP2C19 Poor Metabolisers

Patients who are poor metabolisers of UGT2B17 and CYP2C19 had higher belzutifan AUC [See *Section 5.1 Pharmacodynamic properties*].

Paediatric

No studies with belzutifan have been performed in paediatric patients.

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 Pharmacodynamic properties*].

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

Belzutifan is a substrate of UGT2B17, CYP2C19 and CYP3A4. Active transport is not an important determinant of belzutifan disposition. Belzutifan is not an inhibitor of CYP enzymes, UGT enzymes, or transporters with the exception of MATE2K. Belzutifan does not induce CYP1A2 or CYP2B6, however, WELIREG induces CYP3A4 in a concentration dependent manner.

In Vivo Assessment of Drug Interactions

In a clinical study, repeat administration of WELIREG 120 mg QD resulted in a 40% reduction in midazolam AUC, an effect consistent with a weak CYP3A4 inducer. Based on PBPK modeling, WELIREG may exhibit moderate CYP3A4 induction in patients who have higher belzutifan plasma exposures [See *Section 4.5 Interaction with other medicines* and *other forms of interaction* and *Section 5.1 Pharmacodynamic properties*].

5.3 Preclinical safety data

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 toxicity

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.

Carcinogenesis

Carcinogenicity studies have not been conducted with belzutifan.

Mutagenesis

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

Reproduction

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 [See *Section 5.3 Preclinical safety data, Chronic toxicity]*. There were no findings in female reproductive organs in either rat or dog 3-month toxicity studies.

Development

In a rat embryo-fetal development study, administration of belzutifan during organogenesis caused embryo-fetal lethality up to 100%, reduced fetal body weight, and fetal skeletal abnormalities at exposures similar to or below the human exposure at the recommended dose of 120 mg daily. Based on the observed embryo-fetal lethality in rats treated with belzutifan, a pre- and postnatal developmental toxicity study was not conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each Welireg film-coated tablet contains the following inactive ingredients:
Croscarmellose sodium
Hypromellose acetate succinate
Magnesium stearate
Mannitol
Microcrystalline cellulose
Silicon dioxide

The film-coat contains:
Indigo carmine aluminium lake
Macrogol
Polyvinyl alcohol-part hydrolysed
Talc
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Each carton contains Aluminium/Aluminium foil blisters.

Pack containing 90 (3 packs of 30) film-coated tablets.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription only medicine.

8. SPONSOR

Merck Sharp & Dohme (New Zealand) Limited

PO Box 99-851 Newmarket Auckland 1149

New Zealand

Telephone: 0800 500 673

9. DATE OF FIRST APPROVAL

11 December 2025

10. DATE OF REVISION OF THE TEXT

13 May 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.5	Update to provide additional information to prescribers when administering WELIREG to patients who are dual UGT2B17 and CYP2C19 poor metabolisers
4.9	Update to reflect the highest dosage of WELIREG studied

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