ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets

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 tablet, approximately 13 x 8 mm, debossed with markings “177” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma (RCC)

WELIREG is indicated as monotherapy for the treatment of adult patients with advanced clear cell renal cell carcinoma that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies.

von Hippel-Lindau (VHL) disease-associated tumours

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

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 belzutifan (three 40 mg tablets) administered once daily, at the same time every day.

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, another dose should not be taken. The next dose should be taken the next day.

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

Table 1: Recommended dose modifications

Adverse reactions	Severity*	Dose modification
Anaemia *(see section 4.4)*	Grade 3 (haemoglobin < 8 g/dL; < 4.9 mmol/L; < 80 g/L; transfusion indicated)	• 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 (life-threatening consequences or urgent intervention indicated)	• 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)*	Grade 3 asymptomatic (decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or Pa O_2 ≤ 55 mm Hg))	• 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 (decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or Pa O_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 airway compromise; urgent intervention needed (e.g., tracheotomy or intubation))	• 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) depending on the severity and persistence

Adverse reactions	Severity*	Dose modification
		• 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 5.0

Special populations

Elderly
No dose adjustment is recommended in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is recommended in patients with renal impairment including end-stage renal disease (see section 5.2).

Hepatic impairment
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) or moderate (total bilirubin within range of > 1.5 x ULN and ≤ 3 x ULN and any AST or Child-Pugh B) hepatic impairment. Belzutifan has not been studied in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy in children less than 18 years of age have not been established (see section 5.1). No data are available.

Method of administration

WELIREG is for oral use.

The tablets should be swallowed whole and may be taken with or without food. Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of belzutifan.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy in patients with VHL disease-associated tumours (see section 4.6).

4.4 Special warnings and precautions for use

Anaemia

Anaemia has been reported in patients receiving belzutifan in clinical studies (see section 4.8). Patients should be monitored for anaemia before initiation of and periodically throughout treatment with belzutifan. For patients who develop Grade 3 anaemia, belzutifan should be withheld and patients should be treated according to standard medical practice, including erythropoiesis-stimulating agent (ESA) administration until resolved to ≤ Grade 2 (see the prescribing information for ESAs for more information). For recurrent Grade 3 anaemia, belzutifan should be discontinued. For patients who develop Grade 4 anaemia, belzutifan should be withheld and permanently discontinued for recurrent Grade 4 anaemia (see section 4.2).

Hypoxia

Hypoxia has been reported in patients receiving belzutifan in clinical studies (see section 4.8).

Patients should be monitored for oxygen saturation with pulse oximetry before initiation of and periodically throughout treatment with belzutifan. For Grade 3 asymptomatic 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 symptomatic hypoxia, belzutifan should be withheld, hypoxia should be treated, and belzutifan should be resumed at a reduced dose. If symptomatic hypoxia continues to recur, treatment should be discontinued. For Grade 4 hypoxia, treatment should be permanently discontinued (see section 4.2).

Embryo-foetal toxicity: Women of childbearing potential

Belzutifan may cause embryo-foetal harm, including foetal loss, in humans (see sections 4.6 and 5.3). The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with belzutifan.

Women of childbearing potential have to use highly effective contraceptive methods during treatment with belzutifan and for at least 1 week after the last dose due to the potential risk to the foetus (see sections 4.5 and 4.6).

CNS haemorrhage in patients with VHL disease-associated CNS-haemangioblastomas (CNS-HB)

CNS haemorrhage, including with fatal outcome, has been observed in patients with VHL disease-associated CNS-HB. Physicians should be cautious of symptoms or signs of CNS haemorrhage in patients with VHL disease-associated CNS-HB being treated with belzutifan.

Information about excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, 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, and that belzutifan induces CYP3A4 in a concentration dependent manner.

Effects of belzutifan on other medicinal products

Coadministration of belzutifan 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 5.2). Coadministration of belzutifan with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate should be avoided. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dose in accordance with its summary of product characteristics.

Coadministration of belzutifan with hormonal contraceptives may lead to contraceptive failure (see sections 4.4 and 4.6) or an increase in breakthrough bleeding. 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.

In a clinical study, repeat administration of belzutifan 120 mg daily resulted in a 40% reduction in midazolam area under the curve (AUC), an effect consistent with a weak CYP3A4 inducer. Belzutifan may exhibit moderate CYP3A4 induction in patients who have higher belzutifan plasma exposures (see section 5.2).

Based on *in vitro* data, MATE- 2K inhibition by belzutifan is expected at clinically relevant exposures, and inhibition of MATE1 cannot be excluded.

Belzutifan is a CYP2B6 and CYP2C8 inducer *in vitro. In vivo* investigations have not been performed. Co-administration with belzutifan may result in a clinically relevant decrease in the plasma concentration of sensitive CYP2B6 and/or CYP2C8 substrates.

Effects of other medicinal products on belzutifan

Coadministration 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. Patients should be monitored for anaemia and hypoxia and the dose of belzutifan should be reduced as recommended.

Effects of strong CYP2C19 inducers on belzutifan exposure have not yet been studied.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

The pregnancy status of women of childbearing potential should be verified prior to initiating treatment with belzutifan.

Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman (see sections 4.4 and 5.3). Women of childbearing potential should be informed of the potential risk to a foetus.

Women of childbearing potential have 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 4.5).

Pregnancy

There are no or limited amount of data from the use of belzutifan in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Renal cell carcinoma
Belzutifan should not be used during pregnancy unless the clinical condition of the woman requires treatment with belzutifan.

von Hippel-Lindau (VHL) disease-associated tumours
Belzutifan is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during treatment with belzutifan, treatment should be discontinued.

Breast-feeding

There are no data on the presence of belzutifan or its metabolites in human milk, their effects on the breast-fed child, or on milk production. Because of the potential for serious adverse reactions in breast-fed children, advise women not to breast-feed during treatment with belzutifan and for 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). Patients should be advised of this potential risk. The reversibility of the effect on fertility is unknown.

4.7 Effects on ability to drive and use machines

Belzutifan has 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 has been evaluated in 576 patients with advanced solid tumours and VHL disease-associated localised tumours treated with 120 mg belzutifan once daily in clinical studies. The median duration of exposure to belzutifan was 9.2 months (range: 0.1 to 55.4 months).

The most common adverse reactions under treatment with belzutifan were anaemia (84.2%), fatigue (42.7%), nausea (24.1%), dyspnoea (21.4%), dizziness (17.9%) and hypoxia (16.3%).

The most common Grade 3 or 4 adverse reactions were anaemia (28.8%) and hypoxia (12.2%). The most common serious adverse reactions were hypoxia (7.1%), anaemia (4.7%) and dyspnoea (1.2%).

The most common adverse reactions resulting in dose interruption of belzutifan were anaemia (7.1%), hypoxia (5.4%), fatigue (2.6%), nausea (2.4%), dyspnoea (1.7%) and dizziness (1.6%). The most common adverse reactions resulting in dose reduction of belzutifan were hypoxia (6.3%), anaemia (3.8%) and fatigue (1.7%). The most common adverse reaction resulting in discontinuation of belzutifan was hypoxia (1.4%).

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with belzutifan (n=576) or reported from post-marketing use are listed in Table 2. 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 2: Adverse reactions in patients treated with belzutifan*

Adverse drug reaction	All Grades	Grade 3 – 4
Blood and lymphatic system disorders		
Anaemia†	Very common	Very common
Nervous system disorders		
Dizziness	Very common	-
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Very common	Common
Hypoxia	Very common	Very common
Vascular disorders		
Haemorrhage‡#	Very common	Common
Gastrointestinal disorders		
Nausea	Very common	Uncommon
General disorders and administration site conditions		
Fatigue	Very common	Common
Investigations		
Weight increased	Common	Common

*Adverse reaction frequencies presented in Table 2 may contain contributions from the underlying disease.
†Anaemia includes anaemia and haemoglobin decreased.
‡ Includes different bleeding events from different sites not listed individually.
Haemorrhage terms that occurred in 5 or more patients treated with belzutifan were: haematuria, haemoptysis, contusion and epistaxis (any grade); and haematuria (grades 3-4).
#Includes CNS haemorrhage (a fatal case was observed) (see section 4.4).

Description of selected adverse reactions

Anaemia (see section 4.4)
Anaemia occurred in 83% of patients with advanced RCC receiving belzutifan, 32% had Grade 3 and 0.5% had Grade 4 anaemia. Median time to onset of anaemia was 29 days (range: 1 day to 27 months). Of the patients with anaemia, 22% received transfusions only, 20% of patients received ESAs only and 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 (see section 5.1).

Anaemia occurred in 90.2% of patients with VHL disease-associated tumours receiving belzutifan, 11.5% of patients had Grade 3 anaemia. Median time to onset of all Grade anaemia events was 30 days (range: 1 day to 8 months). Of the patients with anaemia, 1.8% received transfusions only, 16.4% received ESAs only and 9.1% of patients received both transfusion and ESAs. 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).

The incidence of Grade 3 anaemia increased with higher belzutifan exposure in patients with baseline haemoglobin levels < 12 g/dL (see section 4.4).

Hypoxia (see section 4.4)
Hypoxia occurred in 15% of patients with advanced RCC receiving belzutifan and 10% of patients had Grade 3 hypoxia and 0.3% patients had Grade 4 hypoxia. Of the patients with hypoxia, 70% were treated with oxygen therapy. Median time to onset of hypoxia was 31 days (range: 1 day to 21 months).

Hypoxia (Grade 3) was reported in 1.6% of patients with VHL disease-associated tumours receiving belzutifan. Time to onset of hypoxia was 56 days.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, other antineoplastic agents. ATC code: L01XX74

Mechanism of action

Belzutifan is an inhibitor of the transcription factor hypoxia-inducible factor 2 alpha (HIF-2α). Under normal oxygen levels, HIF-2α is targeted for degradation by VHL protein. Impairment of VHL protein function results in accumulation of HIF-2α. Consequently, HIF-2α translocates into the nucleus and regulates expression genes, associated with cellular proliferation, angiogenesis, and tumour 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 transcription and expression of HIF-2α target genes.

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 belzutifan (mean percent decrease from baseline of approximately 60%). Mean EPO levels gradually returned to baseline values after 12 weeks of treatment.

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

Clinical efficacy

Clinical study 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 inhibitors 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. The study excluded patients with hypoxia, active CNS metastases and clinically significant cardiac disease. 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, 369 patients received two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies. The baseline characteristics of those patients were: median age 63 years (range: 33 to 82 years), 40 % age 65 or older; 11 % age 75 or older; 79 % male; 78 % White; 12 % Asian; 1 % Black or African American; 42 % ECOG performance status 0 and 56 % ECOG performance status 1. Prior lines of therapies: 17 % of patients had 2 , 81 % had 3 and 2 % had 4 prior lines of 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.
In the overall population, the study demonstrated statistically significant improvements of PFS (HR: 0.75 [95% CI 0.63, 0.90], p-Value 0.00077) and ORR (21.9% versus 3.5%, p-Value < 0.00001) for patients randomised to belzutifan compared with everolimus at a pre-specified interim analysis (median follow-up time of 13.5 months [range: 0.2 to 31.8 months]).

Table 3 summarises key efficacy measures in the subgroup of patients that received two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies in LITESPARK-005. The KM curves for PFS and OS are shown in Figures 1 and 2.

Table 3: Efficacy results (BICR assessment) in LITESPARK-005 for patients that received two or more lines of therapy that included a PD-(L)1 inhibitor and at least two VEGF-targeted therapies

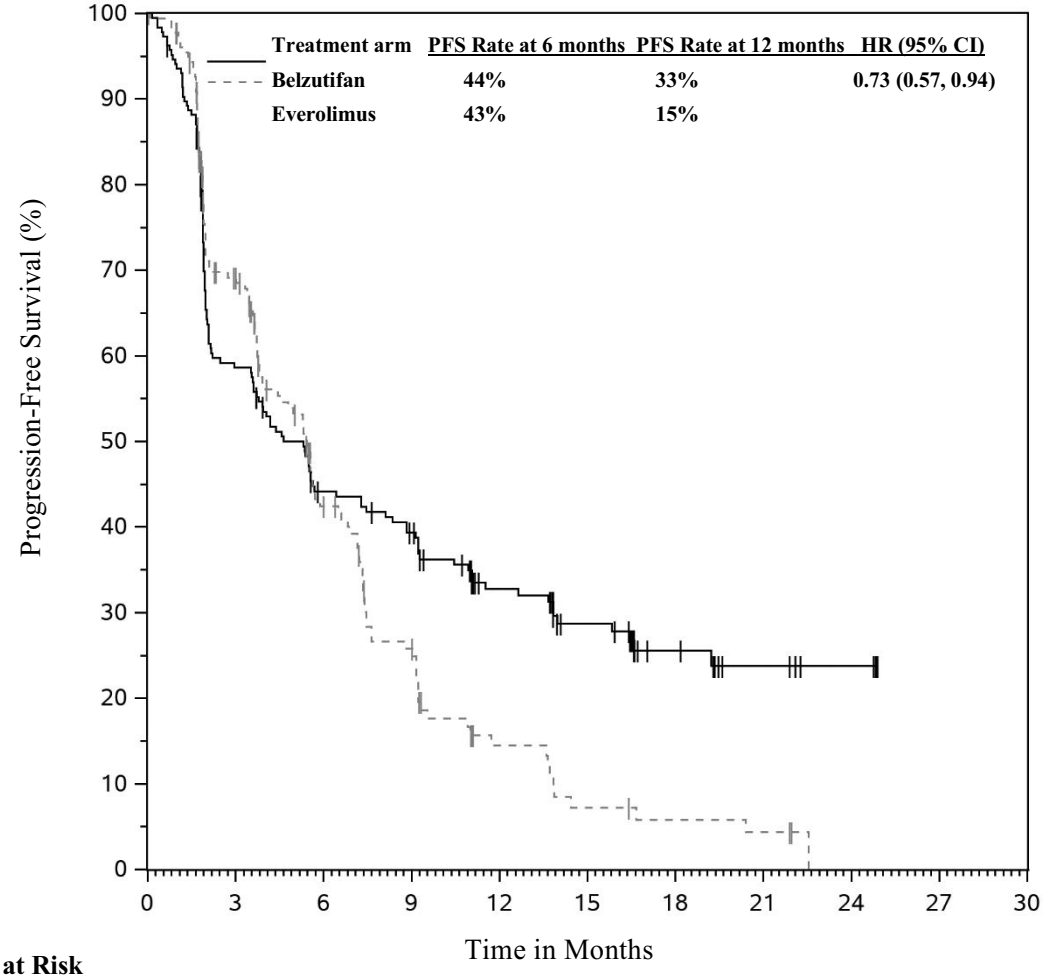
Endpoint	**Belzutifan n=187**	**Everolimus n=182**
PFS[*]		
Number of events, n (%)	127 (67.9%)	130 (71.4%)
Median[†] PFS in months (95% CI)	4.6 (3.5, 7.3)	5.4 (3.8, 6.5)
Hazard ratio[‡] (95% CI)	0.73 (0.57, 0.94)	
OS[¶]		
Number of events, n (%)	128 (68.1%)	125 (68.7%)
Median[†] OS in months (95% CI)	21.8 (17.4, 25.8)	18.1 (14.2, 23.9)
Hazard ratio[‡] (95% CI)	0.94 (0.74, 1.21)	
ORR[*] **%** (95% CI)	24.1% (18.1, 30.8)	3.3% (1.2, 7.0)
Complete response, n (%)	5 (2.7%)	0 (0%)
Partial response, n (%)	40 (21.4%)	6 (3.3%)
Response duration[*]		
Median in months (range)	NR (1.9+, 23.1+)	17.2 (3.8, 17.2)

[*] Based on first pre-specified interim analysis (median follow-up time of 13.5 months)
[†] From product-limit (Kaplan-Meier) method for censored data
[‡] Based on Cox regression model
[¶] Based on final analysis (median follow-up time of 19.6 months)
+ Denotes ongoing response
NR = Not reached

The median time to response (TTR) was 3.7 months (range: 1.7- 16.6) in the belzutifan arm and 3.0 months (range: 1.8- 5.4) in the everolimus arm (median follow-up time of 13.5 months), in the subgroup of patients that received two or more lines of therapy that included a PD-L(1) inhibitor and

at least two VEGF-targeted therapies in LITESPARK-005.

Figure 1: Kaplan-Meier curve for progression-free survival by treatment arm in LITESPARK- 005 for patients that received two or more lines of therapy that included a PD- (L)1 inhibitor and at least two VEGF-targeted therapies*

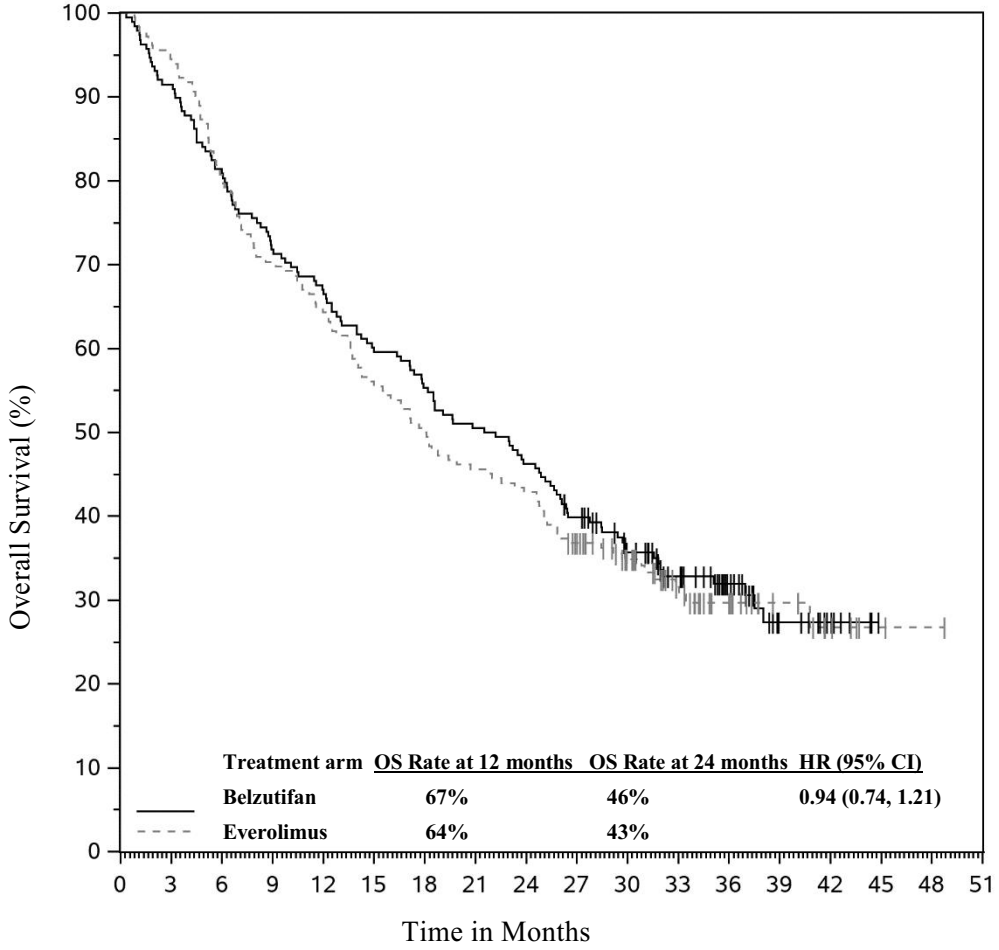


Number at Risk

Belzutifan	187	104	74	64	43	30	15	8	5	0	0
Everolimus	182	107	54	30	12	6	4	3	0	0	0

* Median follow-up time of 13.5 months

Figure 2: Kaplan-Meier curve for overall survival by treatment arm in LITESPARK-005 for patients that received two or more lines of therapy that included a PD- (L)1 inhibitor and at least two VEGF-targeted therapies*



Number at Risk

Belzutifan	188	172	152	135	125	112	104	95	87	73	57	43	28	13	7	0	0	0
Everolimus	182	172	146	128	117	101	92	83	78	64	49	34	22	12	6	2	1	0

* Median follow-up time of 19.6 months

Clinical study in adult patients with von Hippel-Lindau (VHL) disease-associated tumours
The efficacy of belzutifan was investigated in LITESPARK-004, an open-label Phase 2 clinical study 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 could also have other VHL disease-associated tumours, such as CNS haemangioblastomas and pNET. 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. Patients were required to have an ECOG PS of 0 or 1. 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 enrolment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease-associated RCC.

Among the 61 patients enrolled in LITESPARK-004, the population characteristics were: median age of 41 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. Other VHL disease-associated tumours in patients included pancreatic lesions (100.0%) of which 36.1% were pancreatic neuroendocrine tumours, CNS haemangioblastomas (82.0%), and retinal angiomas (19.7%).

The primary efficacy endpoint for the treatment of VHL disease-associated RCC was ORR measured by radiology assessment using RECIST v1.1 as assessed by a central independent review committee (IRC). Additional efficacy endpoints included DOR and TTR. ORR and DOR in other VHL disease-associated tumours were assessed as secondary efficacy endpoints.

Table 4 summarises the efficacy results for VHL disease-associated RCC tumours in LITESPARK-004, based on an interim analysis with a median follow-up time of 49.7 months.

Table 4: Efficacy results in VHL disease-associated RCC tumours in LITESPARK-004

Endpoint	**Belzutifan n=61**
ORR[*] % (95% CI)	67.2% (54.0, 78.7)
Complete response	11.5%
Partial response	55.7%
Response duration[†]	
Median in months (range)	NR (8.6+, 44.4+)
% with duration ≥ 12 months	100.0%
Time to response	
Median in months (range)	11.1 (2.7, 41.2)

Efficacy data with a median follow-up of 49.7 months (cut-off date 3 Apr 2023)
[*] Response: Best objective response as confirmed complete response or partial response
[†] Based on Kaplan-Meier estimates
+ Denotes ongoing response
NR = Not reached

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

Table 5: Efficacy results for belzutifan for other VHL disease-associated tumours

	Belzutifan n=61	
Endpoint	**Patients with evaluable CNS haemangioblastomas n=50**	**Patients with evaluable pancreatic neuroendocrine tumours n=22**
ORR[*] % (95% CI)	48% (33.7, 62.6)	90.9% (70.8, 98.9)
Complete response	8.0%	50.0%
Partial response	40.0%	40.9%
Response duration[†]		
Median in months (range)	NR (0.0+, 47.5+)	NR (11.0+, 48.3+)
% with duration ≥ 12 months	95.5%	100.0%

Efficacy data with a median follow-up of 49.7 months (cut-off date 3 Apr 2023)
[*] Response: Best objective response as confirmed complete response or partial response
[†] Based on Kaplan-Meier estimates
+ Denotes ongoing response
NR = Not reached

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with belzutifan in all subsets of the paediatric population in renal neoplasms and VHL disease (see section 4.2 for information on paediatric use).

Conditional approval

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited. The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of belzutifan are similar in healthy subjects and patients with solid tumours including advanced RCC. Based on population PK analysis, the simulated geometric mean steady-state (CV%) C_{max} is 1.5 mcg/mL (46%) and AUC_{0-24hr} is 20.8 mcg•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 belzutifan, 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, belzutifan 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 belzutifan is 45%. The blood-to-plasma concentration ratio of belzutifan is 0.88.

Biotransformation

Belzutifan is primarily metabolised by UGT2B17 and CYP2C19 and to lesser extent by CYP3A4. Both UGT2B17 and CYP2C19 display genetic polymorphisms (see 'Special populations - *Dual UGT2B17 and CYP2C19 Poor Metabolisers'*).

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 MATE-2K, and potentially MATE1. Belzutifan does not induce CYP1A2, however, belzutifan induces CYP2B6, CYP2C8 and CYP3A4 in a concentration dependent manner (see section 4.5).

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 faeces (primarily as inactive metabolites). Approximately 6% of the dose was recovered as parent drug in urine.

Linearity

The plasma C_{max} and AUC increased proportionally over a dose range of 40 mg to 120 mg.

Special populations

Renal impairment
Based on a population pharmacokinetic analysis of belzutifan in healthy subjects and patients with cancer, no clinically significant differences in the mean belzutifan exposure were observed between subjects with normal renal function and those with mild and moderate renal impairment (as evaluated by estimated glomerular filtration rate (eGFR)). In a dedicated pharmacokinetic study, belzutifan exposure ($AUC_{0\text{-}INF}$) decreased by 6% and increased by 14% in patients with end-stage renal disease before and after haemodialysis, respectively (see section 4.2).

Hepatic impairment
Based on a population pharmacokinetic analysis of belzutifan in healthy subjects and patients with cancer, no clinically significant differences in the mean belzutifan exposure were observed between subjects with normal liver function (total bilirubin and AST ≤ ULN), and those with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1 to 1.5 x ULN and any AST). In a dedicated pharmacokinetic study, belzutifan exposure ($AUC_{0\text{-}INF}$) increased by 52% in patients with moderate hepatic impairment (Child-Pugh B). Patients with severe hepatic impairment have not been studied (see section 4.2).

Dual UGT2B17 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 and 4.8).

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. In patients who are dual UGT2B17 and CYP2C19 poor metabolisers, CYP3A4 may be a major elimination pathway. 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.

Effects of age, gender, ethnicity, race, and body weight
Based on a population pharmacokinetic analysis, age (range: 19 to 90 years), gender, ethnicity, race, and body weight (range: 42.1 to 166 kg) 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 'Special populations - *Dual UGT2B17 and CYP2C19 Poor Metabolisers'*).

5.3 Preclinical safety data

Repeat dose toxicity

Repeat-dose oral toxicity studies in rats and dogs for up to 3 months duration revealed anaemia at all doses including at exposure levels lower than the human exposure levels. Although the anaemia was reversible, this is relevant to humans.

Carcinogenesis

A 26-week transgenic rasH2 mouse carcinogenicity study has been conducted with belzutifan at doses up to 600 mg/kg/day, corresponding to exposures up to 28-fold the human exposure at the approved dose. No belzutifan-related neoplastic findings were observed at any dose level and no carcinogenic risk was identified in the study.

Mutagenesis

Belzutifan was not genotoxic in *in vitro* bacterial mutagenesis and micronucleus assays, and an *in vivo* rat micronucleus assay at 1.7-fold human exposure.

Reproductive toxicity

Fertility studies with belzutifan have not been conducted. In the 3-month repeat-dose toxicity study in rats, irreversible testicular atrophy/degeneration and oligospermia was observed 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. There were no findings in female reproductive organs in either rat or dog 3-month toxicity studies, but HIF-2α has a functional role in the uterus during embryo implantation and establishment of pregnancy in mice. HIF-2α inhibition by exposure to belzutifan has the potential to interfere with embryo implantation, leading to impairment of female fertility.
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Hypromellose acetate succinate
Cellulose microcrystalline (E460)
Mannitol (E421)
Croscarmellose sodium (E468)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E470b)

Film-coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol (E1521)

Talc (E553b)
Indigo carmine aluminium lake (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blisters.

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/001
EU/1/24/1893/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of WELIREG in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the guide for health care professionals, including communication media, distribution modalities, and any other aspects of the safety advice tool, with the National Competent Authority. The patient card is included in the pack.

The safety advice tools are aimed at informing about appropriate contraceptive measures to prevent pregnancies in female patients treated with belzutifan.

The MAH shall ensure that in each Member State where WELIREG is marketed, all healthcare professionals and female patients of childbearing potential who are expected to prescribe or use WELIREG, respectively, have access to/are provided with the following educational package:

- Guide for healthcare professionals
- Patient card

Educational material for healthcare professionals:

- The Summary of Product Characteristics
- Guide for healthcare professionals

Guide for healthcare professionals:

- Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman.
- Belzutifan is contraindicated in pregnant women treated for von Hippel-Lindau (VHL) disease-associated tumours.
- Belzutifan should not be used during pregnancy in women treated for renal cell carcinoma unless the clinical condition requires treatment with belzutifan.
- Details on how to reduce the potential risk of exposure during pregnancy for women of childbearing potential based on the following:
    - o A pregnancy test should be performed before start of treatment with belzutifan.
    - o Women of childbearing potential have to use highly effective contraception method during treatment with belzutifan and up to at least 1 week after the last dose.
    - o Explain to patient that belzutifan may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a condom.
    - o The female patients of childbearing potential should be informed about the potential risk of embryo-foetal harm and appropriate contraceptive measures before start of treatment with belzutifan.
- Need to discontinue treatment with belzutifan if a pregnancy is planned or a pregnancy is detected.
- A patient card is included in the pack. Healthcare professionals should inform each female patient of childbearing potential prior to the start of treatment about the purpose of the patient card.

Patient card:

- Belzutifan should not be used by pregnant women because the use of belzutifan can cause foetal harm, including foetal loss, when used during pregnancy.
- Language describing how to reduce the potential risk of exposure during pregnancy based on the following:
    - o A pregnancy test should be performed before start of treatment with belzutifan.
    - o Women of childbearing potential have to use highly effective contraception method during treatment with belzutifan and up to at least 1 week after the last dose.
    - o Belzutifan may reduce the efficacy of hormonal contraceptives. Therefore, a non-hormonal contraceptive method should be used or have their male partner use a condom.
    - o If a pregnancy occurs during treatment with belzutifan contact your treating physician immediately.
- Contact details of the belzutifan prescriber.
- Women of childbearing potential should be instructed to talk to their healthcare professional about contraception while taking belzutifan.
- Instruct patient to refer to PIL for additional information about the safety of belzutifan.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of belzutifan as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised renal cell carcinoma (RCC), central nervous system (CNS) haemangioblastomas, or pancreatic neuroendocrine tumours (pNET), and for whom localised procedures are unsuitable, the MAH should submit the final results of the ongoing study MK-6482-004, an open-label Phase II single-arm study to further investigate the long-term efficacy and safety of belzutifan for the treatment of von Hippel-Lindau disease-associated Renal Cell Carcinoma.	Q1 2027
In order to confirm the efficacy and safety of belzutifan as monotherapy for the treatment of adult patients with von Hippel-Lindau disease who require therapy for associated, localised RCC, CNS haemangioblastomas, or pNET, and for whom localised procedures are unsuitable, the MAH should submit efficacy and safety data from at least 64 patients with at least 24 months follow-up of cohort B1 for the ongoing study MK-6482-015, an uncontrolled Phase II study to evaluate the efficacy and safety of belzutifan in patients with von Hippel Lindau disease-associated tumours who have at least 1 measurable RCC, pNET, or pheochromocytoma/paraganglioma (PPGL) tumour.	Q1 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets
belzutifan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg belzutifan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/001 30 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

WELIREG 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON OF MULTIPACK – INCLUDING BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets
belzutifan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg belzutifan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
Multipack: 90 (3 packs of 30) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/002 Multipack: 90 (3 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

WELIREG 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF MULTIPACK – WITHOUT BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg film-coated tablets
belzutifan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 40 mg belzutifan.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
30 film-coated tablets
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1893/002 Multipack: 90 (3 packs of 30) film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

WELIREG 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

WELIREG 40 mg tablets
belzutifan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PATIENT CARD

Welireg ▼ (belzutifan)

- Do not take WELIREG for von Hippel-Lindau disease if you are pregnant.
- If you are pregnant and need treatment for Renal Cell Carcinoma (RCC), talk to your doctor about the use of WELIREG.
- WELIREG may harm the baby and may cause a miscarriage. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- Your doctor will do a pregnancy test before you start taking WELIREG.
- You should not become pregnant while taking WELIREG.

Birth control (contraception)

- If you are a woman who could get pregnant:
  - Birth control methods that contain hormones-such as birth control pills, injections, or transdermal patches-may not work as well while you are taking WELIREG.
  - While you are taking WELIREG and for at least 1 week after your last dose you should:
    - Use an effective form of non-hormonal birth control (contraception) or
    - Have your male partner use a condom.
- Talk to your doctor or pharmacist about birth control methods that may be right for you while you are taking WELIREG.
- Tell your doctor immediately if you become pregnant or think you might have become pregnant during treatment.

For more information, consult the Package Leaflet for WELIREG containing information for the patient.

Important Contact Information

Name of Doctor _____
Office Phone _____
After-hours Phone_____
My Name _____

[MSD logo]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

WELIREG 40 mg film-coated tablets
belzutifan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- The pack also contains a patient card intended for women who could get pregnant. Please read it as it contains important safety information you need to be aware of before and during your treatment with WELIREG.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What WELIREG is and what it is used for

WELIREG is a cancer medicine that contains the active substance belzutifan.
WELIREG is used to treat adults with:
- renal cell carcinoma (RCC) with a clear cell component, a type of kidney cancer. It is used when the cancer is advanced (has spread) following treatments that target the immune system (PD-1 or PD-L1 inhibitor) and cancer blood vessels (VEGF-targeted therapy).
- von Hippel-Lindau (VHL) disease (a genetic condition that causes tumours and cysts to grow in certain parts of the body) who need treatment for renal cell carcinoma (RCC), tumours in the brain and spinal cord called central nervous system haemangioblastomas, or a type of pancreatic cancer called pancreatic neuroendocrine tumour, and for whom surgery or other local procedures are unsuitable.

The active substance in WELIREG, belzutifan, blocks a protein called hypoxia-inducible factor 2 alpha (HIF-2α). This protein helps control how cells and blood vessels grow, which can play a role in the development and spread of tumours in the body.

2. What you need to know before you take WELIREG

Do not take WELIREG
- if you are allergic to belzutifan or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor or pharmacist if you are not sure.
- if you are pregnant and need to be treated for von Hippel-Lindau disease (see section 'Pregnancy').

Warnings and precautions
Talk to your doctor or pharmacist before taking WELIREG:
- if you have breathing problems
- if you have low levels of red blood cells (anaemia)
- if you have von Hippel-Lindau disease and tumours in the brain and spinal cord

Low levels of red blood cells (anaemia)

Treatment with WELIREG can cause anaemia (low levels of red blood cells). Tell your doctor if you develop any of the following symptoms:
- shortness of breath
- feeling tired (fatigue)
- dizziness
- pale skin

Your doctor will monitor you for anaemia before you start treatment with WELIREG and during treatment. If you develop severe anaemia your doctor may begin treatment with medicines known to stimulate the production of red blood cells (erythropoiesis-stimulating agents) and/or blood transfusion and stop treatment with WELIREG until the anaemia resolves or they may permanently stop treatment with WELIREG.

Lower oxygen levels in your blood (hypoxia)

Treatment with WELIREG can cause hypoxia. Tell your doctor immediately if you develop any of the following symptoms:
- shortness of breath
- fast heartbeat
- rapid breathing
- bluish discolouration of the skin around your mouth
- inability to speak in full sentences without catching your breath
- unusual tiredness
- confusion

Your doctor will monitor you for hypoxia before you start treatment with WELIREG and during treatment. If you develop severe hypoxia, your doctor may begin treatment with oxygen therapy or stop treatment with WELIREG. Treatment with WELIREG will be restarted at a lower dose. If it recurs, your doctor will discontinue treatment with WELIREG.
In some cases, if you develop hypoxia that is very severe, your doctor may permanently discontinue treatment with WELIREG.

Bleeding in your brain and spinal cord (central nervous system haemorrhage)

Treatment with WELIREG for von Hippel-Lindau disease may cause bleeding in your brain and spinal cord if you have tumours in the brain and/or spinal cord. Tell your doctor immediately if you develop any of the following symptoms:
- severe headache
- vision problems
- severe sleepiness
- severe weakness on one side of your body
- uncoordinated muscle movements
- severe pain in the neck or back
- loss of sensation of pain, temperature and touch

Children and adolescents
WELIREG is not recommended for children and adolescents under 18 years of age. It is unknown if WELIREG is safe and effective for use in these patients.

Other medicines and WELIREG
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because WELIREG can affect the way some other medicines work. Also, some other medicines can affect the way WELIREG works.
WELIREG may affect the way hormonal contraceptives work. While you are taking WELIREG and for at least 1 week after your last dose you should:
- use an effective form of non-hormonal birth control (contraception) or
- have your male partner use a condom.

Pregnancy
Do not take WELIREG for von Hippel-Lindau disease if you are pregnant.
If you are pregnant and need treatment for RCC, talk to you doctor about the use of WELIREG.
WELIREG may harm the baby and may cause a miscarriage. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Your doctor will do a pregnancy test before you start taking WELIREG.
You should not become pregnant while taking WELIREG.

If you are a woman who could get pregnant:
- birth control methods that contain hormones - such as birth control pills, injections, or transdermal patches - may not work as well while you are taking WELIREG.
- while you are taking WELIREG and for at least 1 week after your last dose you should
    - use an effective form of non-hormonal birth control (contraception) or
    - have your male partner use a condom.

Talk to your doctor or pharmacist about birth control methods that may be right for you while you are taking WELIREG.

Fertility
WELIREG may cause fertility problems in men and women, which may affect your ability to have children. Talk to your doctor or pharmacist if this is a concern for you.

Breast-feeding
Tell your doctor or pharmacist if you are breast-feeding or plan to breast-feed.
It is unknown if WELIREG passes into your breast milk. Taking this medicine when you are breast-feeding may harm your baby. You and your doctor should decide together if you will take WELIREG or if you will breast-feed. Do not do both at the same time. If you want to start breast-feeding, wait at least 1 week after your last dose of WELIREG.

Driving and using machines
You may feel dizzy or tired while taking WELIREG. If this happens, do not drive or use machines until you no longer feel dizzy or tired.

WELIREG contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

3. How to take WELIREG

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The recommended dose is 120 mg once daily. Take three 40 mg tablets once a day, at about the same time every day.
- Your doctor may lower your dose or stop treatment, either for a short time or permanently if you experience certain side effects while you are taking WELIREG (see section 4).

How to take
Swallow the tablets whole – do not break them up. It is not known if this medicine works if the tablets are not whole.
You can take WELIREG with or without food.

If you take more WELIREG than you should
If you take too many tablets, contact a doctor or hospital for advice.

If you forget to take WELIREG
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 dose. Take your regular dose of WELIREG the next day.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

WELIREG may cause the following side effects, which may be serious (see section 2):
- reduced levels of red blood cells (anaemia) (very common, may affect more than 1 in 10 people)
- lower oxygen levels in your blood (hypoxia) (very common, may affect more than 1 in 10 people)
- have difficulty breathing (dyspnoea) (very common, may affect more than 1 in 10 people)

Tell your doctor if you feel any of the following symptoms:
- feeling tired (fatigue)
- pale skin
- shortness of breath
- trouble breathing
- chest pain
- a fast heartbeat
- or dizziness

You may need a blood transfusion if your red blood cell counts are too low. You may need supplemental oxygen if your blood oxygen levels are too low.

Your doctor will do blood tests to check your red blood cell counts and measure blood oxygen level before and during your treatment with WELIREG.

Other side effects that may occur:

Very common (may affect more than 1 in 10 people):
- feeling tired (fatigue)
- feeling dizzy
- feeling sick (nausea)
- bleeding (haemorrhage) (including bleeding in your brain and spinal cord if you have von Hippel-Lindau disease associated-central nervous system haemangioblastomas)

Common (may affect up to 1 in 10 people):
- weight gain

Tell your doctor or pharmacist if you notice any of the side effects listed above.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store WELIREG

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister foil and the carton after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if the packaging is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What WELIREG contains
* The active substance is belzutifan. Each film-coated tablet contains 40 mg of belzutifan.
* The other ingredients are croscarmellose sodium (E468) (see "WELIREG contains sodium" in section 2), hypromellose acetate succinate, magnesium stearate (E470b), mannitol (E421), cellulose microcrystalline (E460), and colloidal anhydrous silica (E551). The film-coat contains indigo carmine aluminium lake (E132), macrogol (E1521), polyvinyl alcohol (E1203), talc (E553b), titanium dioxide (E171).

What WELIREG looks like and contents of the pack
WELIREG is a blue, oval film-coated tablet, debossed with 177 on one side and plain on the other side. WELIREG is available in aluminium/ aluminium blisters. Each pack contains 30 film-coated tablets. Each multipack contains 90 (three packs of 30) film-coated tablets. Not all pack sizes may be available in your country.

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This leaflet was last revised in

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine. The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

ANNEX IV

CONCLUSIONS ON THE GRANTING OF THE CONDITIONAL MARKETING AUTHORISATION

Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.