swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Welireg

International non-proprietary name: belzutifan

Pharmaceutical form:	film-coated tablets
Dosage strength(s):	40 mg
Route(s) of administration:	oral
Marketing authorisation holder:	MSD Merck Sharp & Dohme AG
Marketing authorisation no.:	68531
Decision and decision date:	extension of therapeutic indication approved on 1 July 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

1L	First-line
2L	Second-line
3L	Third-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BICR	Blinded independent central review
BOR	Best overall response
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FA	Final analysis
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IA	Interim Analysis
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICI	Immune checkpoint inhibitor
Ig	Immunoglobulin
IMDC	International Metastatic RCC Database Consortium
INN	International non-proprietary name
ITT	Intention-to-treat
KPS	Karnofsky Performance Status
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics

PD	Pharmacodynamics
PD-1/L1	Programmed cell death 1/ligand 1
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PS	Performance status
PSP	Pediatric study plan (US FDA)
QD	Once daily
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension of the therapeutic indication
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Welireg is indicated for the treatment of adult patients with advanced renal cell carcinoma (RCC) following immune checkpoint and anti-angiogenic therapy.

2.2.2 Approved indication

Advanced renal cell carcinoma (RCC)
Welireg as monotherapy is indicated for the treatment of adult patients with unresectable advanced clear cell renal cell carcinoma (RCC) that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and a VEGF tyrosine kinase inhibitor.

2.2.3 Requested dosage

No change to the recommended dosage was requested as part of the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	28 May 2024
List of Questions (LoQ)	21 October 2024
Response to LoQ	21 January 2025
Preliminary decision	17 March 2025
Response to preliminary decision	12 May 2025
Labelling corrections and/or other aspects	16 June 2025
Response to labelling corrections and/or other aspects	24 June 2025
Final decision	1 July 2025
Decision	approval

3 Medical context

Renal cancer is the 14th most common malignancy worldwide, with >430 000 new cases diagnosed in 2020. The incidence varies geographically, with the highest incidence occurring in Western countries (138,611 new cases in Europe in 2020). Renal cell carcinoma (RCC) accounts for approximately 90% of all renal cancers, and represents around 3% of all cancers. During the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe. In 2022, worldwide mortality from RCC was 179,368 deaths (115,600 men and 63,768 women), with a calculated global age-standardised rate of 1.8/100,000[1,2].

Despite the meaningful progress achieved in the first-line (1L) setting of advanced RCC with the introduction of combined immune checkpoint inhibitor (ICI) and anti-vascular endothelial growth factor (VEGF) therapies, outcomes in patients with advanced RCC who have received prior treatment with ICI and VEGF tyrosine kinase inhibitor (TKI) remain poor, with median overall survival (OS) of approximately 18 months[3].

[1] Powles T et al. Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of Oncology 2024;35:692-706.

[2] Ljungberg B et al. EAU Guidelines on Renal Cell Carcinoma 2024.

[3] NCCN Guidelines Kidney Cancer Version 2.2025 – September 6, 2024

4 Nonclinical aspects

4.1 Nonclinical conclusions

The applicant did not submit any new nonclinical studies to support the requested new indication, which is considered acceptable. The new indication is unlikely to result in any significant risk to the environment. From the nonclinical point of view, there are no objections to the approval of the proposed new indication.

5 Clinical aspects

5.1 Clinical pharmacology

PK data from the new patient population were evaluated in a PopPK analysis, which indicated that the PK in the newly requested patient population are consistent with previously approved patient populations.

5.2 Dose finding and dose recommendation

No dedicated dose finding study was conducted. The applicant justified this by referring to the approved belzutifan dosage of 120 mg once daily (QD) in Von Hippel-Lindau (VHL) disease, where RCC is the most frequent tumour type; the efficacy and safety of 120 mg QD belzutifan in clinical studies, including pivotal study LITESPARK-005; and exposure-response relationships for efficacy and safety. The justification was accepted.

5.3 Efficacy

In support of the present application, data from pivotal, open-label, randomised phase 3 study 6482-005 (LITESPARK-005) were submitted. Data from the prespecified analyses interim analysis 1 (IA1; data cut-off (DCO) 01-NOV-2022), IA2 (DCO 13-JUN-2023) and from the final analysis (FA) as of DCO 15-APR-2024 were provided.

In pivotal study LITESPARK-005, belzutifan was compared to everolimus in 746 patients with unresectable, locally advanced, or metastatic clear cell RCC that had progressed after programmed cell death (ligand) 1 (PD-1/L1) ICI and VEGF-TKI therapies (either sequentially or in combination). Patients could have received up to 3 prior treatment regimens and were required to have measurable disease according to RECIST v1.1.

Patients were excluded from the study if they had hypoxia (including the need for supplemental oxygen), inadequate organ function (including haemoglobin <10 g/dL, thrombocytopenia, neutropenia, coagulation markers >1.5x ULN, serum creatinine >1.5x ULN, moderate to severe liver dysfunction), a Karnofsky Performance Status (KPS) score <70%, CNS metastases and/or carcinomatous meningitis, clinically significant heart disease, uncontrolled hypertension, active HBV infection or a history of it, live vaccination within the last 30 days prior to randomisation, and immunodeficiency or immunosuppressive therapy.

Patients were randomised at a ratio of 1:1 and received 120 mg belzutifan or 10 mg everolimus orally QD. Randomisation was stratified based on the International Metastatic RCC Database Consortium (IMDC) risk categories (favourable vs. intermediate vs. poor) and the number of prior VEGF receptor-targeted therapies (1 vs. 2-3).

The baseline characteristics of the 746 patients assigned to randomised treatment in study LITESPARK-005 (374 to belzutifan, 372 to everolimus) were as follows: median age was 63 years (range: 22–90 years), with 42% aged 65 years or older. 78% of the patients were male. 79% were white, 12% were Asian, and 1.1% were black or African American. 43% of the patients had an ECOG Performance Status (PS) of 0, and 55% had an ECOG PS of 1. In terms of prior therapies, 43% had received 2 prior lines of therapy, and 43% had received 3 prior lines. 50.5% of the patients had previously received 1 VEGF receptor-targeted therapy, and 49.5% had received 2 to 3 VEGF receptor-targeted therapies. Prior therapies included cabozantinib (50.7%) and lenvatinib (1.7%). The distribution of patients according to IMDC risk categories was 22% favourable, 66% intermediate, and 12% poor.

The primary efficacy endpoints were progression-free survival (PFS), assessed by blinded independent central review (BICR) using RECIST v1.1, and OS. The objective response rate (ORR), assessed by BICR using RECIST v1.1, was a secondary efficacy endpoint.

The study showed a statistically significant improvement in PFS and ORR for patients randomised to receive belzutifan compared to everolimus.

The hazard ratio (HR) for PFS was 0.75 (95% confidence interval (CI) 0.63, 0.90). The median PFS was 5.6 months in both arms, with a 95%CI of 3.9 to 7.0 months for belzutifan and 4.8 to 5.8 months for everolimus. Disease progression occurred in 63% of patients in the belzutifan arm and 60% in the everolimus arm. More patients were censored early for PFS in the everolimus arm. Of the patients who were censored early, fewer died in the everolimus arm than in the belzutifan arm, suggesting informative censoring. However, the impact of informative censoring on PFS could not be quantified based on the available data, as no further imaging scans were collected after new anticancer therapies were initiated in the patients who were censored early.

ORR was 22% in the belzutifan arm (95%CI 17.8, 26.5), and 3.5% in the everolimus arm (95%CI 1.9, 5.9). Complete response was 2.7% in the belzutifan arm and 0% in the everolimus arm. Partial response was 19% in the belzutifan arm and 3.5% in the everolimus arm. In the Best Overall Response (BOR) analysis, a higher rate of progressive disease (PD) was reported in the belzutifan arm than in the everolimus arm (33.7% versus 21.5%).

For OS, the final analysis after a median follow-up of 19.6 months and at an OS maturity of 69% showed no statistically significant difference between the two arms (HR 0.92; 95%CI 0.77, 1.10).

5.4 Safety

Although the percentages of patients with any adverse event (AE), AEs of grade ≥3 to 5, and serious AEs were comparable across both arms of pivotal study LITESPARK-005, the safety profile of belzutifan compared favourably with everolimus in terms of the lower percentage of patients with AEs necessitating treatment discontinuation and the lower number of grade 5 AEs. No new safety signals were reported for belzutifan. Updated safety results submitted in response to the LoQ were consistent with the earlier results that formed the basis of the clinical assessment.

However, as a prerequisite for granting authorisation, additional safety labelling in the Information for healthcare professionals was requested for musculoskeletal pain, constipation, herpes zoster, grade 3-4 increases in liver function tests, falls and fractures, since these were reported more frequently for belzutifan therapy than for everolimus. For further details, refer to the Information for healthcare professionals.

5.5 Final clinical benefit risk assessment

Despite uncertainties regarding the evidence of efficacy, including informative PFS censoring, a higher rate of PD in the belzutifan arm as compared to everolimus in the BOR analysis, and the failure to demonstrate an OS benefit, pivotal study LITESPARK-005 showed a formally positive result for the primary endpoint PFS. In addition, the safety profile of belzutifan compared favourably with everolimus in terms of the lower percentage of patients with AEs that necessitated treatment discontinuation and the lower number of grade 5 AEs. Ultimately, belzutifan treatment offers a therapy with a different mechanism of action and safety profile than other available systemic therapies (VEGF-TKIs and everolimus), expanding treatment options that can be individualised to a patient's comorbidities and preferences. Considering all these aspects, benefit-risk balance was judged to be positive once the indication was restricted to the 3L+ setting and after prior VEGF-TKI therapy had been specified in line with the eligibility and population of the pivotal study.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Welireg was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

IMPORTANT WARNING on the use of WELIREG:

- **Exposure to Welireg during pregnancy can cause embryo-foetal harm.**
- **Verify pregnancy status prior to the initiation of Welireg.**
- **Advise patients of these risks and the need for effective non-hormonal contraception. Welireg can render some hormonal contraceptives ineffective (see “Interactions” and “Pregnancy, lactation”).**

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Welireg has temporarily authorized indications, see “Indications/Uses” section.

WELIREG®

Composition

Active substances

Belzutifan

Excipients

Hypromellosum acetas succinas, Cellulosum microcristallinum (E 460), Mannitolum (E 421), Carmellosum natricum connexum (E 468), Silica colloidalis anhydrica (E 551), Magnesii stearas (E 470b), Polyalcohol vinylicus (E 1203), Titanii dioxidum (E 171), Macrogolum 3350 (E 1521), Talcum (E 553b), Indigocarminum (E 132).
Each film-coated tablet contains maximum 1.356 mg of sodium.

Pharmaceutical form and active substance quantity per unit

Each film-coated tablet contains 40 mg of belzutifan.

Indications/Uses

Temporarily authorized indication
von Hippel-Lindau (VHL) disease associated tumors
Welireg as monotherapy is indicated for the treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for VHL associated renal cell carcinoma (RCC), central nervous system

(CNS) hemangioblastomas, or pancreatic neuroendocrine tumours (pNET), not requiring immediate surgery.

There are no data on metastatic VHL-associated tumors (see “Clinical Efficacy”).

These indications have been granted temporary authorisation as the clinical data were incomplete at the time the application was assessed (Art. 9a Therapeutic Products Act). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be converted into an ordinary authorisation.

Indication with non-limited authorization

Advanced Renal Cell Carcinoma (RCC)

Welireg as monotherapy is indicated for the treatment of adult patients with unresectable advanced clear cell renal cell carcinoma (RCC) that progressed following two or more lines of therapy that included a PD-(L)1 inhibitor and a VEGF tyrosine kinase inhibitor.

Dosage/Administration

Initiation of treatment

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

Usual dosage

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

Duration of therapy

It is recommended that therapy be continued until disease progression or unacceptable toxicity occurs. For the maximum duration of exposure of belzutifan treatment in clinical trials, please refer to the study description (see “Clinical Efficacy”).

Dose adjustment following undesirable effects/interactions

Dosage modifications for Welireg for adverse reactions are summarised in Table 1 (see “Warnings and precautions”).

Table 1: Recommended Dose Modifications

Adverse Reactions	Severity*	Dose Modification
Anaemia *(see “Warnings and precautions”)*	Grade 3: Haemoglobin (Hgb <8g/dL) transfusion indicated	• Withhold until resolved to ≤ Grade 2 (Hb ≥8 g/dL). • 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 or	• Withhold until resolved to ≤ Grade 2 (Hb ≥8 g/dL).

Adverse Reactions	Severity*	Dose Modification
	urgent intervention indicated	• Resume at a reduced dose (reduce by 40 mg) or permanently discontinue.
Hypoxia *(see "Warnings and precautions")*	Grade 2: Decreased oxygen saturation with exercise (e.g. pulse oximeter <88%) intermittent supplemental oxygen	• Consider withholding until resolved • Resume at the same dose or at a reduced dose depending on the severity of hypoxia.
	Grade 3: Decreased oxygen saturation at rest (e.g. pulse oximeter <88% or PaO^2 <=55 mm Hg)	• Withhold until resolved to ≤ Grade 2 • Resume at reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of hypoxia.
	Grade 4: Life-threatening	• Permanently discontinue.
Other Adverse Reactions *(see "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 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0

Special dosage instructions

Patients with hepatic disorders

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

Patients with renal disorders

No dose adjustment of Welireg is recommended in patients with renal impairment, including end-stage renal disease. Patients with severe renal impairment should be monitored for increased adverse reactions and the dosage adjusted as recommended (see "Pharmacokinetics").

Elderly patients

No dose adjustment is recommended for elderly patients (65 years and older) (see "Pharmacokinetics").

Children and adolescents

The safety and efficacy in children less than 18 years have not been established. No data are available.

Delayed administration

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

Mode of administration

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition”.

Warnings and precautions

Anaemia due to decreased erythropoietin
Anaemia occurred very commonly in patients receiving Welireg (see “Undesirable effects”). Patients should be monitored for anaemia before initiation of and periodically throughout treatment with belzutifan with more frequent monitoring within the first 6 months of treatment (see “Properties/Effects”). Dose adjustments should be made according to Table 1 (see “Dosage/Administration”).
The efficacy and safety of erythropoiesis stimulating agents (ESAs) for treatment of anaemia in patients treated with Welireg have not been established. Randomized controlled trials in patients with cancer receiving myelosuppressive chemotherapy with ESAs have shown that ESAs increased the risks of death and serious cardiovascular reactions, and decreased progression-free survival and/or overall survival. See the prescribing information for ESAs for more information.
Hypoxia
Belzutifan can cause severe hypoxia that may require discontinuation, supplemental oxygen, or hospitalisation (see “Dosage/Administration”).
Patients should be monitored for oxygen saturation with pulse oximetry before initiation of and periodically throughout treatment with belzutifan with more frequent monitoring within the first 6 months of treatment (see “Properties/Effects”). In light of the risk of hypoxia, smoking cessation is recommended.
For Grade 2 hypoxia, providing supplemental oxygen and continuing or withholding treatment should be considered. If withheld, belzutifan should be resumed at a reduced dose. For patients who have Grade 3 hypoxia, belzutifan should be withheld, hypoxia treated, and dose reduction should be

considered. If Grade 3 hypoxia continues to recur, treatment should be discontinued. For Grade 4 hypoxia, treatment should be permanently discontinued (see “Dosage/Administration”).

Embryo-foetal toxicity

Based on findings in animals, belzutifan may cause foetal harm, including foetal loss, in humans. In a rat study, belzutifan caused embryo-foetal toxicity up to 100% when administered during the period of organogenesis at maternal exposures that were similar to or lower than the human exposures at the recommended dose of 120 mg daily (see “Preclinical data”).

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

Patients treated with belzutifan must be given the patient card.

Fertility

Belzutifan may impair fertility in males and females of reproductive potential (see “Pregnancy, lactation”). The reversibility of the effect on fertility is unknown.

Excipients

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium free’.

Interactions

Effect of belzutifan on other medicinal products

CYP3A4 substrates

In a clinical study, repeat administration of belzutifan 120 mg QD resulted in a 40% reduction in midazolam AUC, an effect consistent with a weak CYP3A4 inducer. Based on PBPK modeling, belzutifan may exhibit moderate CYP3A4 induction in patients who have higher belzutifan plasma exposures (see “Properties/Effects”).

Co-administration of belzutifan with CYP3A4 substrates, including hormonal contraceptives, decreases concentrations of CYP3A4 substrates (see “Properties/Effects” and “Pharmacokinetics”), which may reduce the efficacy of these substrates.

Avoid co-administration of belzutifan with sensitive CYP3A4 substrates, for which minimal decrease in concentration may lead to therapeutic failures of the substrate. If co-administration cannot be avoided,

increase the sensitive CYP3A4 substrate dosage in accordance with its summary of product characteristics.

Hormonal contraceptives

Co-administration of belzutifan with hormonal contraceptives may lead to contraceptive failure or an increase in breakthrough bleeding.

Other interactions

Based on in vitro studies, belzutifan is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 enzymes and does not induce CYP1A2 or CYP2B6.

Based on in vitro studies, belzutifan inhibits MATE2K but not P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or MATE1.

Effect of other medicinal products on belzutifan

Based on in vitro and/or pharmacogenetic studies, belzutifan is a substrate of UGT2B17, CYP2C19, CYP3A4 and P-gp.

UGT2B17 or CYP2C19 inhibitors

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

Pregnancy, lactation

Women of child-bearing potential / contraception in males and females

Pregnancy Testing

The pregnancy status of females of reproductive potential should be verified prior to initiating treatment with belzutifan.

Contraception

Belzutifan may cause embryo-foetal harm, including foetal loss, when administered to a pregnant woman (see “Warnings and precautions” and “Preclinical data”).

Females

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

Males

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

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

Pregnancy

There are no data from the use of belzutifan in pregnant women. Studies in animals have shown reproductive toxicity (see “Preclinical data”). Belzutifan should not be taken during pregnancy and in women of childbearing potential not using contraception.

Lactation

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

Fertility

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

Effects on ability to drive and use machines

Belzutifan may have an influence on the ability to drive and use machines. Dizziness, fatigue, and nausea may occur following administration of belzutifan (see “Undesirable effects”).
Patients should be advised not to drive and use machines, until they are reasonably certain belzutifan therapy does not affect them adversely.

Undesirable effects

Summary of the safety profile

The safety assessment of belzutifan is based on the pooled safety data of 576 patients from four clinical studies, study 001 (58 patients), study 004 (61 patients), study 005 (381 patients including Japanese patients) and study 013 (76 patients), using the recommended dose of 120 mg belzutifan once daily in patients with advanced solid tumours, VHL-associated RCC and advanced RCC.
The median duration of exposure to belzutifan was 9.2 months (range: 0.1 to 55.4 months).
The most common adverse reactions with belzutifan were anaemia (83%), fatigue (43%), musculoskeletal pain (38%), nausea (24%), dyspnoea (21%), constipation (18%), dizziness (18%), and hypoxia (16%).
The most common Grade 3 or 4 adverse reactions were anaemia (29%), and hypoxia (12%).
Serious adverse reactions occurred in 12% of patients who received belzutifan, including hypoxia (7.1%), anaemia (4.7%) and dyspnoea (1.2%).

Dose interruption of belzutifan due to adverse reactions occurred in about 18% of patients. The most common adverse reactions resulting in dose interruption of belzutifan were anaemia (7.1%), hypoxia (5.4%), fatigue (2.6%) and nausea (2.4%).

Dose reduction of belzutifan due to adverse reactions occurred in about 12% of patients. The most common adverse reactions resulting in dose reduction of belzutifan were hypoxia (6.3%), anaemia (3.8%) and fatigue (1.7%).

Discontinuation of belzutifan due to adverse reactions occurred in about 2.3% of patients. The most common adverse reaction resulting in discontinuation of belzutifan was hypoxia (1.4%).

List of adverse reactions

Adverse reactions reported in clinical studies of belzutifan are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), and not known (frequency cannot be estimated from the available data).

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

Adverse Drug Reaction	All Grades	Grade 3 – 4
Blood and lymphatic disorders		
Anaemia	Very common (84%)	Very common (29%)
Metabolism and nutrition disorders		
Hyperglycaemia	Common	Common
Weight increased	Common	Common
Nervous system disorders		
Headache	Very common (19%)	Uncommon
Dizziness	Very common (18%)	Not known
Eye disorders		
Retinal vein occlusion	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Visual impairment	Common	Not known
Vascular disorders		
Hypertension	Common	Common
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Very common (21%)	Common
Hypoxia	Very common (16%)	Very common (12%)
Gastrointestinal disorders		

Nausea	Very common (24%)	Uncommon
Constipation	Very common (18%)	Uncommon
General disorders and administration site disorders		
Fatigue	Very common (43%)	Common
Infections and infestations		
Herpes zoster	Common	Not known
Injury, poisoning and procedural complications		
Fall	Common	Not known
Fracture*	Common	Common
Investigations		
Alanine aminotransferase increased	Very common (14%)	Common
Aspartate aminotransferase increased	Very common (12%)	Common
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	Very common (38%)	Common

*The following terms represent a group of related events that describe a medical condition rather than a single event:

- Fracture (spinal compression fracture, hip fracture, humerus fracture, pathological fracture, ankle fracture, facial bones fracture, fracture, pelvic fracture, scapula fracture, spinal fracture, thoracic vertebral fracture, upper limb fracture, femur fracture, fractured sacrum, hand fracture, radius fracture, rib fracture, shoulder fracture)
- Musculoskeletal pain (arthralgia, back pain, myalgia, muscle spasms, chest pain, chest discomfort)

Description of specific adverse reactions and additional information

Anaemia due to decreased erythropoietin (see "Warnings and precautions")

In the pooled safety set, anaemia was reported in 84% of all patients with Grade 3-4 anaemia occurring in 29%. Median time to onset of all Grade anaemia events was 51.7 days (range: 1 day to 27.4 months). Forty-one (7.1%) participants had anaemia events leading to study drug interruption and 22 participants (3.8%) had a dose reduction due to anaemia. Two participants (0.3%) discontinued treatment due to anaemia. Anaemia was reported as resolved in 165 (34%) of participants and not yet resolved in 249 (51%) participants.

Hypoxia (see "Warnings and precautions")

In the pooled safety set, hypoxia occurred in 94 patients (16%), with grade 3-4 hypoxia occurring in 70 patients (12%). Thirty-one (5.4%) participants had hypoxia events leading to study drug interruption, 36 participants (6.3%) had a dose reduction due to hypoxia, and 8 (1.4%) patients discontinued treatment due to hypoxia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very 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 ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for belzutifan overdose. In cases of suspected overdose, withhold belzutifan and institute supportive care. The highest dose of belzutifan studied clinically was 240 mg daily (120 mg twice a day or 240 mg once a day). Adverse reactions observed in patients receiving more than 120 mg once a day were generally similar to those observed at other doses except for Grade 3 hypoxia observed at 120 mg twice a day and Grade 4 thrombocytopenia observed at 240 mg once daily.

Properties/Effects

ATC code

L01XX74

Mechanism of action

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

Pharmacodynamics

Circulating plasma levels of 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.

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 little to no enzyme activity. Approximately 15% of Caucasians, 11% of Latinos, 6% of African Americans, 38% of South Asians, and 70% of East Asians are UGT2B17 poor metabolisers. Approximately 2% of Caucasians, 1% of Latinos, 5% of African Americans, 8% of South Asians, and 13% of East Asians are CYP2C19 poor metabolisers. Approximately 0.3% of Caucasians, 0.1% of Latinos, 0.3% of African Americans, 3% of South Asians, and 9% of East Asians are dual UGT2B17 and CYP2C19 poor metabolisers.
The impact of CYP2C19 and UGT2B17 poor metabolisers on belzutifan exposure was assessed in a population PK analysis. Based on the 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 tumors
The efficacy of belzutifan was investigated in Study 004 (LITESPARK-004), an open label Phase 2 clinical study in 61 patients with confirmed VHL disease, based on a VHL germline alteration, who had at least one measurable solid tumour (as defined by RECIST v1.1) localised to the kidney and who did not require immediate surgery. Enrolled patients had other VHL-associated tumours including CNS haemangioblastomas and pNET, identified by radiological appearance. The study excluded patients who had any evidence of metastatic disease, either RCC or other VHL disease associated tumours. Other exclusion criteria were immediate need for surgical intervention for tumour treatment, any major surgical procedure completed within 4 weeks prior to study enrolment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease associated RCC. Patients were monitored for anaemia and hypoxia before initiation of belzutifan, and

then every 2 weeks for the first month, monthly for the next 5 months, and then every 3 months thereafter throughout treatment.

The study population characteristics were: median age of 41 years [range 19-66 years], 3.3% age 65 or older; 52.5% male; 90.2% White; and 82.0% had an ECOG PS of 0 and 16.4% had an ECOG PS of 1. Seventy-seven percent of patients had prior RCC surgical procedures encompassing ablative procedures, partial nephrectomy, radical nephrectomy.

The median diameter of RCC target lesions per central independent review committee (IRC) was 2.2 cm (range 1-6.1). Ten patients had baseline RCC target lesion diameters >3cm. Median time from initial radiographic diagnosis of VHL associated RCC tumours that led to enrolment on Study 004 to the time of treatment with Welireg was 17.9 months (range 2.8-96.7).

Patients received belzutifan at a dose of 120 mg once daily. Patients were evaluated radiologically approximately 12 weeks after initiation of treatment and every 12 weeks thereafter while continuing on study treatment for a minimum of 3 years. After 3 years, patients will be evaluated radiologically every 24 weeks thereafter, or more frequently if clinically indicated. Treatment was continued until progression of disease or unacceptable toxicity. The effect of intermittent use and long treatment interruptions of belzutifan has not been studied.

The primary efficacy endpoint for the treatment of VHL disease associated RCC was overall response rate (ORR) measured by radiology assessment using RECIST v1.1 as assessed by IRC. Secondary efficacy endpoints included duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), time to response (TTR), and time to surgery (TTS).

Table 3 summarises the efficacy results for VHL disease associated RCC tumours in Study 004 after a median follow-up time of 37.7 months (range 4.2-46.1). The median duration of exposure was 37.3 months (range 1.9-46.1).

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

Endpoint	**Belzutifan 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)	Not reached (5.4+, 35.8+)

% with duration ≥24 months	86.6%
Time to response	
Median in months (range)	11.1 (2.7, 30.5)
Time to surgery	
Median in months (95% CI)	Not reached (NR, NR)
PFS‡	
Median in months (95% CI)	Median not estimated§
36-month PFS rate (95% CI)	86.3% (73.2, 93.3

* 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.
NR = Not reached
Data cut-off: April 1, 2022

During this period of treatment, 7 out of 61 (11.5%) patients required an RCC tumour reduction procedure.

Objective response rates in other VHL diseases associated tumours were: 44% CNS haemangioblastomas (95% CI: 30.0, 58.7; 22 out of 50 patients), and 90.9% for pancreatic neuroendocrine tumours (95% CI: 70.8, 98.9; 20 out of 22 patients).

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

The efficacy of belzutifan was evaluated in Study 005 (LITESPARK-005), an open-label, randomized, 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 programmed cell death (ligand) 1 (PD-1/L1) checkpoint inhibitor and VEGF-tyrosine kinase inhibitor therapies (either in sequence or in combination). Patients could have received up to 3 prior treatment regimens and had to have measurable disease per RECIST v1.1. The study excluded patients with hypoxia (including the need for supplemental oxygen), inadequate organ function (including haemoglobin <10g/dL, thrombocytopenia, neutropenia, coagulation marker >1.5x ULN, serum creatinine >1.5x ULN, moderate to severe hepatic impairment), KPS score <70%, CNS metastases and/or carcinomatous meningitis, clinically significant cardiac disease, poorly controlled hypertension, active infection and history of HBV, live vaccine within 30 days prior to randomisation, as well as immunodeficiency or immunosuppressive therapy. Patients were randomized in a 1:1 ratio to receive 120 mg belzutifan or 10 mg everolimus by oral administration once daily. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk categories (favorable versus intermediate versus poor) and number of prior VEGF receptor targeted therapies (1 versus 2-3).

Among the 746 patients in Study 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: 43% had 2 prior lines of therapy and 43% had 3 prior lines of therapy; 50.5% of patients had received 1 prior VEGF receptor targeted therapy and 49.5% received 2 to 3 prior VEGF receptor targeted therapies. Prior therapy included cabozantinib (50.7%) and lenvatinib (1.7%). Patient distribution by IMDC risk categories was 22% favorable, 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 measure was the objective response rate (ORR) assessed by BICR using RECIST v1.1.

The trial demonstrated a statistically significant improvement of PFS and ORR for patients randomized to Welireg compared with everolimus. In the best overall response (BOR) analysis, a higher rate of progressive disease was reported in the belzutifan arm compared to everolimus (33.7% versus 21.5%). The efficacy results of the primary analysis for advanced RCC in Study 005 are summarized in Table 4.

Table 4: Efficacy Results (BICR assessment) for Belzutifan in Study-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	

* Based on first pre-specified interim analysis.
† From product-limit (Kaplan-Meier) method for censored data.
‡ Based on the stratified Cox regression model.

OS did not reach statistical significance at final analysis after a median follow-up duration of 19.6 months (HR 0.92, 95%-CI: 0.77; 1.10; maturity of OS data 69%).

Pharmacokinetics

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 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 belzutifan, peak plasma concentrations (median T_{max}) of belzutifan occurred at 1.5 hours post dose.

Effect of food

A high-fat, high-calorie meal delayed peak belzutifan concentration by approximately 2 hours but, had no effect on exposure (AUC). There was a modest decrease of C_{max} by 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 (29%). Plasma protein binding of belzutifan is 45%. The blood-to-plasma concentration ratio of belzutifan is 0.88.

Metabolism

Belzutifan is metabolized primarily by UGT2B17-mediated glucuronidation and CYP2C19-mediated oxidation and to a lesser extent by CYP3A4. Both UGT2B17 and CYP2C19 display genetic polymorphisms (see “Properties/Effects”).

Elimination

Based on the population PK analysis, the mean (CV%) clearance is 5.89 L/hr (61%) and the mean elimination half-life is approximately 14 hrs.

Following oral administration of radiolabeled 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/non-linearity

C_{max} and AUC increase proportionally over a dose range of 20 mg to 120 mg.

Kinetics in specific patient groups

Hepatic impairment

Based on a population pharmacokinetic analysis of belzutifan in healthy subjects and patients with cancer, no clinically relevant 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 pharmacokinetic study, belzutifan exposure ($AUC_{0\text{-}INF}$) increased by 52% in subjects with moderate hepatic impairment (Child-Pugh B) compared to subjects with normal liver function. Patients with severe hepatic impairment have not been studied (see “Dosage/Administration” and “Pharmacokinetic*s”).*

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 eGFR). In a pharmacokinetic study in patients with end-stage renal disease, belzutifan exposure ($AUC_{0\text{-}INF}$) decreased by 6% when taking belzutifan 2 hours before hemodialysis and increased by 14% when taking belzutifan directly after haemodialysis, respectively, compared to the exposition in subjects with normal renal function (see *"*Dosage/Administration*"* and *"*Pharmacokinetics*"*).

Effects of Age, Gender, Ethnicity, Race, and Body Weight

Based on a population pharmacokinetic analysis, age (19 to 90 years), gender, ethnicity (non-Hispanic, Hispanic), race (White, Black, Asian, Native American, Pacific Islander), and body weight (42 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 "Properties/Effects").

Genetic polymorphisms

Dual UGT2BI7 and CYP2C19 Poor Metabolisers

Patients who are dual UGT2B17 and CYP2C19 poor metabolisers have higher belzutifan exposures, which may increase the incidence and severity of adverse reactions of belzutifan and should be closely monitored (see "Warnings and precautions", "Undesirable effects" and "Properties/Effects").

Preclinical data

Single and repeat dose 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.

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.

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been concluded for belzutifan.

Reproductive toxicity

Fertility

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

Development

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

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Store at 15-30°C.
Keep out of the reach of children.

Authorisation number

68531 (Swissmedic)

Packs

Welireg 40 mg: 90 film-coated tablets (A).

Marketing authorisation holder

MSD MERCK SHARP & DOHME AG

Luzern

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