swissmedic

Date: 7 June 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

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: temporary authorisation in accordance with Art. 9a TPA approved on 21 March 2024

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.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AEs	Adverse events
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
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
BID	Twice daily
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EPO	Erythropoietin
ERA	Environmental risk assessment
ESA	Erythropoietin stimulating agent
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HIF	Hypoxia-inducible factor
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
ICR	Independent central review
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LGR	Linear growth rate
LoQ	List of Questions
MACE	Major adverse cardiovascular events
MAH	Marketing authorisation holder
Max	Maximum
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
Min	Minimum
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
pNET	Pancreatic neuroendocrine tumour

PopPK	Population pharmacokinetics
PPGL	Pheochromocytoma/paraganglioma
PSP	Pediatric study plan (US FDA)
QD	Once daily
QoL	Quality of life
RCC	Renal cell carcinoma
RMP	Risk management plan
RP2D	Recommended phase 2 dose
SAEs	Serious adverse events
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
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)
TTR	Time to response
TTS	Time to surgery
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for belzutifan in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 15 July 2021.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

2.2 Indication and dosage

2.2.1 Requested indication

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

2.2.2 Approved indication

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

There are no data on metastatic VHL-associated tumours (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 (authorisation without special conditions).

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Welireg is 120 mg (3 x 40 mg tablets) administered orally once daily, with or without food. Tablets should be swallowed whole.
Treatment should continue until disease progression or unacceptable toxicity occurs.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	7 July 2022
Formal control completed	5 August 2022
List of Questions (LoQ)	2 December 2022
Response to LoQ	27 March 2023
Preliminary decision	22 June 2023
Response to preliminary decision	4 September 2023
Labelling corrections	23 November 2023
Response to labelling corrections	18 December 2023
Second round labelling corrections	25 January 2024
Second round response to labelling corrections	1 February 2024
Final decision	21 March 2024
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

Swissmedic has only assessed parts of the primary data submitted with this application. As regards the remaining data, Swissmedic relies for its decision on the assessment of the foreign reference authority (MHRA, PLGB 53095/0087, dated 31.05.2022) provided by the applicant, and is adopting the results of the assessment of the foreign reference authority.

3 Medical context

Von Hippel-Lindau disease (VHL) is a hereditary disease, which will invariably lead to the development of several types of tumours. The most frequent are clear cell renal cell carcinomas (RCC), central nervous system (CNS) haemangioblastomas, retinal haemangioblastomas, and pancreatic tumours. Other tumours can also be observed. RCC are malignant and have the potential to metastasise, therefore threatening the patient's life. According to the Danish vHL coordination group (Binderup et al., von Hippel-Lindau disease: Updated guideline for diagnosis and surveillance, European Journal of Medical Genetics, Volume 65, Issue 8, 2022: 104538), the median life expectancy for male VHL patients is 67 years and for female patients 60 years with the current standard of care consisting of surveillance and surgery, when indicated. haemangioblastomas are non-malignant tumours. Depending on the localisation, they can, however, be symptomatic and severely affect the patient's quality of life and are the most frequent cause of VHL-associated death (51% to 76%) together with RCC (16% to 36%). Currently, no prophylactic treatment options are available. Close surveillance and surgery as indicated represent the standard of care. The Danish guideline on diagnosis and surveillance of VHL disease states the following regarding belzutifan: *Although now approved by the FDA, the appropriate use of belzutifan in patients with vHL remains to be determined* (Binderup et al., European Journal of Medical Genetics, Volume 65, Issue 8, August 2022, 104538).

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority (MHRA, PLGB 53095/0087, dated 31.05.2022) provided by the applicant, and is adopting the results of the assessment of the foreign reference authority.

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority (MHRA, PLGB 53095/0087, dated 31.05.2022) provided by the applicant, and is adopting the results of the assessment of the foreign reference authority.

6 Clinical aspects

6.1 Clinical pharmacology

The evaluation of the clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the MHRA and FDA. The available assessment reports and corresponding product information from these authorities were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, see the information for healthcare professionals in the appendix to this report.

6.2 Dose finding and dose recommendation

Study MK-6482-0001 was a dose escalation and expansion trial of belzutifan, a HIF-2α inhibitor, in patients with advanced solid tumours. The primary objective was to identify the maximum tolerated dose (MTD) and/or the recommended phase 2 dose (RP2D) of belzutifan.

Dose levels of 20 mg once daily (QD), 40 mg QD, 80 mg QD, 120 mg QD, 160 mg QD, 240 mg QD, and 120 mg twice daily (BID) were investigated. While the study protocol foresaw enrolment of 3 patients per dose level in the absence of dose-limiting toxicity, all dose levels enrolled 6 patients (except for 120 mg QD, which enrolled 58 patients and 240 mg QD with 7 patients). No MTD was found. Increasing dose resulted in an increase in the average reduction of erythropoietin (EPO), with a mean reduction of 69% at 120 mg QD, demonstrating significant target engagement.

The RP2D of 120 mg QD was selected as the optimal biological dose based on safety (no MTD reached up to 240 mg per day), pharmacokinetics (PK) and pharmacodynamics (PD) considerations of possible plateauing of exposure (C_{max} and $AUC_{0\text{-}tau}$), and PD (EPO) response at this dose.

Nevertheless, given the small patient numbers exposed to lower doses, the efficacy assessment is not conclusive in the opinion of Swissmedic Clinical Assessment. While there were no responses, there were patients with stable disease. Therefore, the question of whether a lower dose may have achieved similar efficacy with a better safety profile remains open.

Since no further efficacy or safety data on lower doses of belzutifan are expected and the pivotal trial in patients with VHL disease has been conducted with the RP2D of 120 mg QD, this dose recommendation is accepted.

6.3 Efficacy

Study MK-6482-004 was conducted in a cohort of 61 patients suffering from VHL disease with at least 1 measurable renal lesion assumed to be clear cell RCC. Histologic confirmation was not required. Patients were young and fit overall. Of the 61 study patients, 48 had undergone at least 1 prior surgical intervention for VHL-associated renal lesions; 26 had had more than 1 renal procedure since diagnosis, with an average of 1728 days (4.73 years) [range: 62 to 6210 days] between procedures. Patients were allowed to enrol regardless of the presence of other VHL-associated tumours. Patients received belzutifan 120 mg QD orally until disease progression or intolerable toxicity. In response to the Swissmedic Clinical Assessment (CA) List of Questions (LoQ), an update with a data cut-off date of 1 April 2022 was provided. The median duration of follow-up at that time was 37.7 months (range: 4.2 to 46.1 months). The primary endpoint of this single-arm, open-label study was the objective response rate (ORR) by independent central review (ICR) for VHL-associated RCC. The study was not designed or powered to evaluate ORR in haemangioblastomas or pancreatic neuroendocrine tumours (pNETs).

The null hypothesis was an ORR of 15% and the alternative hypothesis was an ORR of 30%. The sample size was calculated to be 50 patients to provide greater than 80% power to reject the null hypothesis with a one-sided alpha of 0.05%.

ORR is not an accepted endpoint for a confirmatory trial in this setting. Neither a single-arm trial design nor a one-sided alpha of 0.05% are acceptable in a confirmatory trial. This trial was clearly

exploratory and accordingly has major limitations. In addition, no rationale was provided for the 15% and 30% ORR thresholds used for the sample size calculation. Finally, the study over-enrolled considerably in less than 1 year. This brings into question the applicant's argument that a randomised study would not be feasible in this patient population. Given the study design, the criteria for a confirmatory study according to the ICH E9 guideline are not fulfilled. Therefore, the conditions for a marketing authorisation without special conditions as a first-line treatment are not fulfilled. However, the applicant states that a randomised trial was and is not feasible, arguing that this is due to a lack of equipoise between scientific and patient communities, a risk of unblinding, and patient retention/lack of an appropriate comparator, in particular since belzutifan has now been authorised by other regulators.

The study showed a steadily increasing ORR over time, with an ORR of 59% for renal lesions at 29.2 months of median follow-up. At 37.7 months of follow-up, the response rate was 64%. The study met its primary endpoint.

The secondary endpoints were time to response (TTR), duration of response (DOR), progression-free survival (PFS), time to surgery (TTS), and linear growth rate (LGR). The most relevant endpoints of PFS and TTS were not yet reached. However, given the single-arm design of the study, it will be impossible to draw definitive conclusions from these data.

Study MK-6482-004 did not primarily address non-RCC tumours. The results show tumour shrinkage for CNS haemangioblastoma, which are often symptomatic. In this situation, belzutifan may be a treatment alternative when surgery is not feasible. In particular, haemangioblastomas are often localised in the retina, the cerebellum, and the brain stem. CNS haemangioblastomas are indeed the primary cause of VHL-associated mortality (51% to 76%) (Binderup et. al., J Med Genet. 2017 Jan;54(1):11-18). The importance of belzutifan for the treatment of pNETs is less clear since these tumours are typically non-functional and often asymptomatic.

6.4 Safety

The following safety analysis focuses on the safety data of the 61 VHL patients from study MK-6482-004 and the 58 solid tumour patients from study MK-6482-0001 who had been treated with the recommended 120 mg QD dosage. Only few patients were aged 65 years or older and even fewer patients were 75 years or older. The vast majority of patients were from the US.

In its List of Questions, Swissmedic had requested the inclusion of safety data on all patients exposed to belzutifan irrespective of indication, and that the data should not be limited to belzutifan monotherapy. The safety profile based on the resulting safety pool of in total 576 patients who had been exposed to the recommended 120 mg QD dosage can be found in the approved information for healthcare professionals (see Appendix).

Adverse events

Nearly all patients presented adverse events (AEs) and drug-related AEs. In the VHL cohort, 44% of patients had grade 3-5 AEs at the latest data cut-off date provided with a follow-up of 37.7 months. This percentage was 67% in the solid tumour safety cohorts with more comorbid and older patients (median age 62). Serious AEs (SAEs) were observed in 30% of VHL patients and 43% of solid tumour patients. AEs leading to dose reductions occurred in 16% of VHL and 10% of solid tumour patients. Two patients in the VHL cohort died and 11 patients died in the solid tumour safety dataset (see *Deaths* below).

The most frequent AE in all safety pools was anaemia. Anaemia is an on-target effect (as a reminder, the RP2D was chosen on the basis of a 69% reduction in erythropoietin). Other frequent AEs were fatigue, headache, dizziness, nausea, and dyspnoea in patients with VHL. Patients in study MK-6482-001 with more advanced solid tumours had several additional frequent AEs such as oedema, vomiting, cough, hypoxia (31%), dehydration, and hyperkalaemia. Although these patients were older

and more heavily pre-treated, they had a good performance status at baseline. There were several cases of adrenal insufficiency, including 3 SAEs, and 2 cases of embolism.

In a single-arm study, it will always be difficult to evaluate relatedness to the study drug and bias is inherent based on the safety description in the investigator brochure. However, given the young age of the enrolled VHL patients and their excellent ECOG (Eastern Cooperative Oncology Group) performance status (0 for 82% of them), drug-relatedness appears probable. This is particularly true for AEs observed in high proportions of patients and compatible with the mode of action, such as anaemia and consequently anaemia-related adverse effects.

Grade 3 to 5 adverse events

Grade 3-5 AEs presented in 44% of VHL patients. Given the young age and good performance status at study entry, this proportion is high. Given the absence of a control arm, it is very difficult or even impossible to determine causality. In particular, hypertension, retinal vein occlusion, retinal detachment, and hyperglycaemia are of concern and were therefore labelled in the information for healthcare professionals.

Given the high incidence of anaemia, a number of patients received red blood cell transfusions. However, there were also patients receiving EPO-stimulating agents (ESA). Studies have shown that patients with malignant tumours receiving ESA for anaemia treatment had a higher risk of death and major adverse cardiovascular events (MACE). Although no deaths or MACE considered related to ESA use in studies MK-6482-001 or MK-6482-004 have been reported, the follow-up is too short to conclude that this treatment is safe. Indeed, in the solid tumour cohort 1 patient died of a cardiac arrest and 1 of an acute coronary syndrome. In addition, 2 patients in the VHL cohort developed malignancies (non-small cell lung cancer and vulval cancer). Therefore, this argumentation of only restoring physiological EPO levels is considered hypothetical and cannot be accepted.

Serious adverse events

Nearly one third of VHL patients (30%) presented an SAE. This is concerning in a young and fit population. Again, since there is no control arm, it is difficult to assess relatedness. Drug-related SAEs comprise hypoxia, anaemia, urinary tract infection, dyspnoea, and wound dehiscence. In the summary of clinical safety, the complete list of SAEs shows additional events (DCO 01 Jun 2020) such as infectious complications, cardiac complications, respiratory affections, and haemorrhage. Given the known physiological roles of hypoxia-inducible factor (HIF), these AEs could well be related to the study drug.

Deaths

In the solid tumour cohort, 11 deaths, 1 acute kidney injury, 6 malignant neoplasm progressions, 1 acute coronary syndrome, 1 cardiac arrest, 1 suicide, and 1 bowel perforation were described.

Two deaths occurred in the VHL cohort. One patient died due to suicide, the other was judged to have died due to toxicity to multiple agents. An autopsy determined the cause of death as toxicity to various agents (Grade 5). Fentanyl was present in the post-mortem blood, and the neuropathology report showed that acute hypoxic ischaemic changes had occurred. An overdose of fentanyl could be a suicide attempt. In addition, 1 other death in the non-VHL cohort was also due to suicide. The observation of 2 suicides and 1 possible suicide in such a small safety cohort is concerning and requires further follow-up (see below).

Dose interruptions, dose reductions, and treatment discontinuation

Fatigue, likely related to anaemia, was the most common reason for both dose interruptions and dose reductions. For quality of life, this is likely an issue given the prolonged intent of the treatment.

AEs leading to treatment discontinuation comprised dizziness and hypoxia.

Other safety concerns

Reproductive toxicity was observed in both male and female animals in preclinical studies, including irreversible changes in male reproductive organs. The submitted documentation mentions analyses

for male reproductive hormones in 29/32 male VHL patients. Only aggregate summaries are provided about the number of patients with normal, high, or low levels of respective hormones. Only 12 men had paired semen analyses and of these, more (6/12) showed a decrease in total sperm count than an increase (3/12). The report provided only gives a written summary and no actual laboratory data. The applicant argues in the report that no conclusions can be drawn given the small numbers. While Swissmedic Clinical Assessment agrees with this, it does not agree that no further investigations are necessary. A warning regarding fertility was included in the information for healthcare professionals.

6.5 Final clinical benefit-risk assessment

Von Hippel-Lindau disease (VHL) is a hereditary disease, which will invariably lead to the development of several types of tumours. The most frequent are clear cell renal cell carcinomas (RCC), central nervous system (CNS) haemangioblastomas, retinal haemangioblastomas, and pancreatic tumours. Other tumours can also be observed. RCC are malignant and have the potential to metastasise, therefore threatening the patient's life. The median life expectancy for male VHL patients is 67 years and for female patients 60 years with the current standard of care consisting of surveillance and surgery, when indicated. Haemangioblastomas are non-malignant tumours. Currently, no prophylactic treatment options are available. Close surveillance and surgery as indicated represent the standard of care.

The data submitted demonstrate that belzutifan decreases the tumour size of renal cell carcinomas (although many not histologically confirmed) as well as other VHL-associated tumours such as CNS haemangioblastomas, retinal haemangioblastomas, and pancreatic neuroendocrine tumours in approximately 64% of patients. Time to response is relatively long at about 35 weeks and varies somewhat between the different tumour types. Median duration of response, median time to next surgery, and median progression-free survival have not been reached.

However, the major limitation of this data is the uncontrolled, single-arm study design. It is impossible to know how patients fare with the standard of care consisting of surveillance or surgery, when necessary, compared to belzutifan. No randomised clinical trial is planned for VHL patients. In addition, among 17 patients who discontinued belzutifan for other reasons than progressive disease, 8 did not show an objective response. However, despite the absence of a response and discontinuation of the study treatment, only 1 patient underwent surgery for a VHL-associated RCC.

Another uncertainty concerns the use of ORR as primary endpoint, although it is not considered a validated endpoint for a confirmatory study in this indication. Furthermore, the dose finding is considered inadequate. The safety profile shows a high incidence of AEs including grade ≥ 3 and SAEs, particularly anaemia, fatigue, nausea, dyspnoea, and hypoxia. Only 61 patients in the overall safety population have the requested indication.

There is 1 randomised controlled trial ongoing in clear cell RCC patients having progressed on a checkpoint inhibitor and an anti-VEGF (vascular endothelial growth factor) agent. In total, 736 patients were planned to be randomised to belzutifan or everolimus. One actively recruiting phase 2 trial is enrolling patients with VHL-associated tumours as well as patients with pheochromocytoma/paraganglioma (PPGL) and pNETs. The primary endpoint is ORR; the secondary endpoints are DOR, TTR, disease control rate (DCR), PFS, and overall survival (OS). There will again be no comparative data, and no quality of life (QoL) data are expected.

In conclusion, the submitted data are considered insufficient for an authorisation without special conditions.

However, the criteria for a temporary authorisation are cumulatively fulfilled, in particular given the high and durable response rate in this disease setting with a high unmet medical need. Further clinical data regarding the durability of responses as well as results from ongoing studies in other VHL-associated tumours need to be submitted as requirements for a transformation into a approval without special conditions. These include additional data from registrational study MK-6482-004 as well as

data from studies in clear cell RCC (MK-6482-005, -018, and -013). Regarding safety, the applicant has been requested to present a comprehensive safety analysis, including suicide and suicidal behaviour.

7 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.

8 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 been authorised temporarily, 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

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.

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 a reduced dose (reduce by 40 mg) or discontinue depending on the severity and persistence of anaemia.
	Grade 4: Life-threatening or urgent intervention indicated	• Withhold until resolved to ≤ Grade 2 (Hb ≥8 g/dL). • Resume at a reduced dose (reduce by 40 mg) or permanently discontinue.
Hypoxia *(see “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	• Withhold until resolved to ≤ Grade 2

Adverse Reactions	Severity*	Dose Modification
	oximeter <88% or PaO^2 <=55 mm Hg)	• 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 4.0

Special dosage instructions

Patients with hepatic disorders

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

Patients with renal disorders

No dose adjustment of Welireg is recommended in patients with mild or moderate renal impairment (eGFR ≥30 mL/minute/1.73 m^2). Welireg has not been studied in patients with severe renal impairment (see "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”). For patients who develop Grade 3 anaemia (Hb < 8 g/dL), belzutifan should be withheld and patients should be treated according to standard medical practice . For recurrent Grade 3 anaemia, belzutifan should be discontinued. For patients who develop Grade 4 anaemia, the dose of belzutifan should be reduced or permanently discontinued (see “Dosage/Administration”).

The use of erythropoiesis stimulating agents (ESAs) for treatment of anemia is not recommended in patients treated with Welireg. For patients treated with Welireg who develop anemia, the safety and effectiveness for use of ESAs 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”). Patients treated with belzutifan must be given the patient card.

Embryo-foetal toxicity

Based on findings in animals, belzutifan may cause foetal harm, including foetal loss, in humans. In a rat study, belzutifan caused embryo-foetal toxicity 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.

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

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

Effect of belzutifan on other medicinal products

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.

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

Effect of other medicinal products on belzutifan

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

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 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 and fatigue 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 13.5 months (range: 0.1 to 55.4 months).
The most common adverse reactions with belzutifan were anaemia (83.2%), 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%).
Serious adverse reactions occurred in 12.2% 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 17.7% 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 11.6% 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 (84.2%)	Very common (28.8%)
Metabolism and nutrition disorders		
Hyperglycaemia	Common	Common
Weight increased	Common	Common
Nervous system disorders		
Headache	Very common (19.1%)	Uncommon
Dizziness	Very common (17.9%)	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 (21.4%)	Common
Hypoxia	Very common (16.3%)	Very common (12.2%)
Gastrointestinal disorders		
Nausea	Very common (24.1%)	Uncommon
General disorders and administration site disorders		
Fatigue	Very common (42.7%)	Common

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 84.2% of all patients with Grade 3-4 anaemia occurring in 28.8%. 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 (16.3%), with grade 3-4 hypoxia occurring in 70 patients (12.2%). 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

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

Pharmacogenomics

Belzutifan is primarily metabolised by UGT2B17 and CYP2C19. The activity of these enzymes varies among individuals who carry different genetic variants, which may impact belzutifan concentrations. Poor metabolisers are individuals who are considered to have no enzyme activity. Approximately 15% of Caucasians, 11% of Latinos, 6% of African Americans, 38% of South Asians, and 70% of East Asians are UGT2B17 poor metabolisers. Approximately 2% of Caucasians, 1% of Latinos, 5% of African Americans, 8% of South Asians, and 13% of East Asians are CYP2C19 poor metabolisers. Approximately 0.3% of Caucasians, 0.1% of Latinos, 0.3% of African Americans, 3% of South Asians, and 9% of East Asians are dual UGT2B17 and CYP2C19 poor metabolisers.
The impact of CYP2C19 and UGT2B17 poor metabolisers on belzutifan exposure was assessed in a population PK analysis. Based on the analysis, VHL disease-associated RCC patients who are UGT2B17, CYP2C19, or dual UGT2B17 and CYP2C19 poor metabolisers, are projected to have 1.5, 1.6 or 2.3 fold the exposures (steady state $AUC_{0\text{-}24hr}$), respectively, compared to a typical reference patient (UGT2B17 intermediate metaboliser, CYP2C19 non-poor metaboliser) for the recommended dose. No dose adjustment is recommended based on exposure response analyses for efficacy and safety and the risk benefit profile.

Clinical efficacy

The efficacy of belzutifan was investigated in Study 004, an open label Phase 2 clinical study in 61 patients with confirmed VHL disease, based on a VHL germline alteration, who had at least one measurable solid tumour (as defined by RECIST v1.1) localised to the kidney and who did not require immediate surgery. Enrolled patients had other VHL-associated tumours including CNS haemangioblastomas and pNET, identified by radiological appearance. The study excluded patients who had any evidence of metastatic disease, either RCC or other VHL disease associated tumours.

Other exclusion criteria were immediate need for surgical intervention for tumour treatment, any major surgical procedure completed within 4 weeks prior to study enrolment, any major cardiovascular event within 6 months prior to study drug administration, or prior systemic treatments for VHL disease associated RCC. Patients were monitored for anaemia and hypoxia before initiation of belzutifan, and then every 2 weeks for the first month, monthly for the next 5 months, and then every 3 months thereafter throughout treatment.

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

The median diameter of RCC target lesions per central independent review committee (IRC) was 2.2 cm (range 1-6.1). 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).

Pharmacokinetics

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

Absorption

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

Effect of food

A high-fat, high-calorie meal delayed peak belzutifan concentration by approximately 2 hours but, had no effect on exposure (AUC). There was a modest decrease of C_{max} by 35% following consumption of

a high-fat, high-calorie meal, but this was not clinically meaningful. Therefore, belzutifan can be taken without regard to food.

Distribution

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

Metabolism

The major metabolic pathways for belzutifan are UGT2B17 mediated glucuronidation and CYP2C19 mediated oxidation. Both UGT2B17 and CYP2C19 display genetic polymorphisms (see "Properties/Effects").

Elimination

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

Linearity/non-linearity

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

Kinetics in specific patient groups

Hepatic impairment

No relevant increase in exposure (AUC) was observed for subjects with mild hepatic impairment (using NCI index) based on population pharmacokinetic analysis. The pharmacokinetics of belzutifan have not been studied in patients with moderate or severe hepatic impairment (see "Dosage/Administration" and "Pharmacokinetic*s").*

Renal impairment

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

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

Based on a population pharmacokinetic analysis, age, gender, ethnicity, race, and body weight do not have a clinically meaningful effect on the pharmacokinetics of belzutifan. Potential differences in exposure across races are possible due to different frequencies of metabolising enzymes (see "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
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