Swiss Summary of the Risk Management Plan (RMP)

Welireg®

(Belzutifan)

Active substance(s): Belzutifan

Product(s) concerned: WELIREG®

Based on GB-RMP V0.4 (May 2022)

Version 1.0 (April 2024)

Marketing Authorisation Holder: MSD Merck Sharp & Dohme AG, Lucerne

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Welireg® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the «Arzneimittelinformation / Information sur le médicament» approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Welireg® in Switzerland is the «Arzneimittelinformation/ Information sur le médicament» (see www.swissmedic.ch) approved and authorized by Swissmedic. MSD Merck Sharp and Dohme AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Welireg®.

Summary of Risk Management Plan for WELIREG® (Belzutifan)

This is a summary of the risk management plan (RMP) for WELIREG. The RMP details important risks of WELIREG, how these risks can be minimised, and how more information will be obtained about risks and uncertainties (missing information) of WELIREG.

The WELIREG GB SmPC and Package Insert give essential information to healthcare professionals and patients on how WELIREG should be used.

Important new concerns or changes to the current GB SmPC and Package Insert will be included in updates of the WELIREG RMP.

I. The Medicine and What It Is Used For

WELIREG is authorised 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), and for whom localised procedures are unsuitable or undesirable. It contains belzutifan as the active substance and it is given by oral administration.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of WELIREG, together with measures to minimise such risks and the proposed studies for learning more about risks of WELIREG, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and GB SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of WELIREG is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of WELIREG are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of WELIREG. Potential risks are concerns for which an association with

the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	Anaemia due to decreased erythropoietin Hypoxia
Important potential risks	Embryo-fetal toxicity
Missing information	Long term safety Safety in moderate to severe hepatic impairment Safety in severe renal impairment

II.B Summary of Important Risks

Table II.B.1: Important Identified Risk: Anaemia Due To Decreased Erythropoietin

Evidence for linking the risk to the medicine	Review of belzutifan non-clinical, clinical trial data and literature regarding anaemia due to decreased erythropoietin represent sufficient evidence of a causal association with belzutifan exposure.
Risk factors and risk groups	There are no known risk factors and risk groups significantly associated with the development of anaemia due to decreased erythropoietin. Baseline anaemia in patients may increase the risk of development of more severe anaemia.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2 (Dosage and Administration), 4.4 (Warning and Precautions) and 4.8 (Undesirable effects) of the SmPC Patient Information Leaflet. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Table II.B.2: Important Identified Risk: Hypoxia

Evidence for linking the risk to the medicine	Review of belzutifan clinical trial data and literature regarding hypoxia represent sufficient evidence of a causal association with belzutifan exposure.
Risk factors and risk groups	There are no known risk factors and risk groups significantly associated with the development of hypoxia.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2 (Dosage and Administration), 4.4 (Warning and Precautions) and 4.8 (Undesirable effects) of the SmPC

Table II.B.2: Important Identified Risk: Hypoxia

	Patient Information Leaflet Additional risk minimisation measures: Patient Alert Card.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Table II.B.3: Important Potential Risk: Embryo-fetal toxicity

Evidence for linking the risk to the medicine	Rat embryo-fetal development study.
Risk factors and risk groups	Female patients of childbearing potential. Male patients with female partners of childbearing potential.
Risk minimisation measures	Routine risk minimisation measures: Section 4.4 and 4.6 of the SmPC Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Table II.B.4: Missing Information: Long Term Safety

Evidence for linking the risk to the medicine	Protocol Study 6482-004 and study 6482-005
Risk factors and risk groups	There are no known risk factors and risk groups significantly associated with long term safety.
Risk minimisation measures	Routine risk minimisation measures: None. Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: To address missing information of long term safety, follow-up safety information will be collected in Studies 6482-004 and 6482-005

Table II.B.5: Missing Information: Safety In Moderate To Severe Hepatic Impairment

Evidence for linking the risk to the medicine	Available preclinical data indicate that belzutifan is anticipated to be predominantly eliminated by hepatic metabolism. Belzutifan has not been studied in patients with moderate to severe hepatic impairment.
Risk factors and risk groups	Patients with moderate to severe hepatic impairment.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2 (Dosage and Administration) of SmPC Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Table II.B.6: Missing Information: Safety In Severe Renal Impairment

Evidence for linking the risk to the medicine	Renal excretion is not anticipated to represent a major clearance route for belzutifan. However, impaired renal function has been demonstrated to alter drug metabolism and transport pathways in the liver and gut, and these effects are more prominent in patients with severely impaired renal function. Belzutifan has not been studied in patients with severe renal impairment.
Risk factors and risk groups	Patients with severe renal impairment.
Risk minimisation measures	Routine risk minimisation measures: Sections 4.2 (Dosage and Administration) of the SmPC Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of WELIREG.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study 6482-004 is an Open-label Phase 2 Study to Evaluate PT2977 for the Treatment of von Hippel-Lindau Disease-associated Renal Cell Carcinoma and its purpose is to evaluate the efficacy and safety of MK-6482 in participants with VHL disease and at least 1 measurable RCC tumor.

Long term safety follow-up will provide information of long term safety of belzutifan, which will further inform its safety profile.

Study 6482-005 is an ongoing open-label, randomized active-comparator controlled Phase 3 study in participants with advanced ccRCC. Participants who have progressed on or after treatment with both PD-1/L1 checkpoint inhibitor and VEGF TKI in sequence or in combination will receive belzutifan 120 mg QD or everolimus 10 mg QD. Participants are to have received no more than 3 prior system regimens for locally advanced or metastatic ccRCC.