Summary of the Risk Management Plan (RMP) for Opsumit® (macitentan)

Marketing Authorisation Holder (MAH): Actelion Pharmaceuticals Ltd.

Document version 2.0

Document date 23-Octt-2024

Based on EU RMP version 15.1, 04-Sep-2024

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 Opsumit® 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 Opsumit® in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Actelion Pharmaceuticals Ltd is fully responsible for the accuracy and correctness of the content of the published summary RMP of Opsumit®.

Summary of Risk Management Plan for OPSUMIT (macitentan)

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

OPSUMIT's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how OPSUMIT should be used.

This summary of the RMP for OPSUMIT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of OPSUMIT's RMP.

I. The Medicine and What it is Used For

OPSUMIT is authorized for the long-term treatment of pulmonary arterial hypertension (PAH) in adult and paediatric patients of World Health Organization (WHO) Functional Class (FC) II to III (see SmPC for the full indication). It contains macitentan as the active substance and it is given orally once daily.

Further information about the evaluation of OPSUMIT's benefits can be found in OPSUMIT's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/opsumit

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of OPSUMIT, together with measures to minimize such risks and the proposed studies for learning more about OPSUMIT's risks, are outlined below.

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

Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorized 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 (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of OPSUMIT, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of OPSUMIT are risks that need special risk management activities to further investigate or minimize 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 OPSUMIT. 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 (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Hepatotoxicity Teratogenicity
Important potential risks	None
Missing information	None

II.B. Summary of Important Risks

Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Macitentan, like other medicines of the same class, may affect the liver. The mechanism of this adverse effect is unclear. Interruption or stopping treatment may be necessary.
Risk factors and risk groups	Unknown in patients with alanine aminotransferase/aspartate aminotransferase >3×upper limit of normal at baseline or patients with moderate or severe liver impairment, as they were excluded from clinical trials with macitentan. Based on postmarketing data, there were no new safety concerns noted in patients with moderate or severe hepatic impairment receiving macitentan.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3 ‘Contraindication’ and PL section 2 ‘What

	you need to know before you take Opsumit' SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.8 'Undesirable Effects' and PL section 4 'Possible side effects' Instructions for liver function monitoring and actions to be taken in case of elevated hepatic enzymes are provided in SmPC Section 4.4 Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: Risk minimization tools (patient card)

Important Identified Risk: Teratogenicity	
Evidence for linking the risk to the medicine	According to results from animal studies, macitentan and medicines of the same class may harm unborn babies conceived before starting or during treatment. Based on a limited number of pregnancies observed in women exposed to macitentan, no translation of this risk to humans has been observed.
Risk factors and risk groups	All women of childbearing potential on macitentan therapy who are not using a reliable method of contraception.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.3 'Contraindication' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.4 'Special Warnings and Precautions for Use' and PL section 2 'What you need to know before you take Opsumit' SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit' Instructions for the use of Opsumit in women of childbearing potential and recommendation for monthly pregnancy tests during treatment are provided in SmPC section 4.4 Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: Risk minimization tools (patient card)

II.C. Postauthorization Development Plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of OPSUMIT.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for OPSUMIT.