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

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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. Janssen-Cilag AG 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 patients of World Health Organization Functional Class 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:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002697/human_med_001717.jsp&mid=WC0b01ac058001d124

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.

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

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	Anemia, decrease in hemoglobin concentration Hepatotoxicity Teratogenicity Symptomatic hypotension
Important potential risks	Menstrual disorders (primarily bleeding) Ovarian cysts Pulmonary edema associated with pulmonary veno-occlusive disease (PVOD) Testicular disorders and male infertility
Missing information	Pediatric patients

II.B. Summary of Important Risks

Important Identified Risk: Anemia, decrease in hemoglobin concentration	
Evidence for linking the risk to the medicine	Macitentan and medicines of the same chemical class may reduce the blood hemoglobin level. Blood transfusion may be required in some cases. In the pivotal Phase 3 study of macitentan in PAH (SERAPHIN), a clinically relevant decrease in hemoglobin concentration was reported in 8.7% of macitentan-treated subjects and 3.4% of placebo-treated subjects.
Risk factors and risk groups	General risk factors for anemia are, eg, iron deficiency, history of anemia, concomitant use of platelet inhibitors, anticoagulants, steroids, and pre-existing or concurrent bleeding.
Risk minimization measures	Routine risk minimization measures: 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' Recommendation to not use Opsumit in patients with severe anemia and recommendation for monitoring of hemoglobin concentration are included in SmPC Section 4.4 Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: None.

Important Identified Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Macitentan, like other medicines of the same chemical 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.
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 chemical 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)

Important Identified Risk: Symptomatic hypotension	
Evidence for linking the risk to the medicine	Macitentan, like other medicines of the same chemical class, widens blood vessels, and blood pressure (BP) decrease has been reported. In a long-term double-blind study (SERAPHIN), decrease of BP was reported in 7.0% of macitentan-treated subjects and 4.4% of placebo-treated subjects. Among patients who receive prescribed macitentan, 1–2 in 100 report symptomatic hypotension. The most frequent clinical sign of hypotension is dizziness. Macitentan may lead to more reduction of BP in patients with kidney problems.
Risk factors and risk groups	Patients with moderate or severe renal impairment.
Risk minimization measures	Routine risk minimization measures: 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' Advice on the use of Opsumit in patients with renal impairment who are at risk of experiencing hypotension and recommendation

	for monitoring blood pressure are provided in SmPC Section 4.4 Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: None.

Important Potential Risk: Menstrual disorders (primarily bleeding)	
Evidence for linking the risk to the medicine	Among female PAH subjects participating in the pivotal clinical study (AC-055-302, SERAPHIN), menstrual disorders (primarily bleeding) occurred in 5.1% of the macitentan 10 mg-treated subjects compared to 1.1% of the placebo-treated subjects. Most of the subjects were receiving anticoagulants and/or other medications with known side effects of bleeding at the same time. At present, a causal relationship between macitentan and menstrual disorders, primary bleeding, is difficult to establish.
Risk factors and risk groups	Risk factors include a previous history of menstrual disorders / bleeding or concomitant treatment with drugs known to cause bleeding. Endocrine causes of menorrhagia include thyroid and adrenal gland dysfunction, pituitary tumors, anovulatory cycles, polycystic ovarian syndrome, obesity, and vasculature imbalance (Shaw 2018).
Risk minimization measures	Routine risk minimization measures: Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: None.

Important Potential Risk: Ovarian cysts	
Evidence for linking the risk to the medicine	Among female PAH subjects participating in the pivotal clinical study (AC-055-302, SERAPHIN), ovarian cysts were reported in few macitentan-treated subjects. Most of these subjects had other diseases known to be risk factors for ovarian cysts, as documented in their medical history. At present, a causal relationship between macitentan and ovarian cyst is difficult to establish.
Risk factors and risk groups	Ovarian cysts can occur at any age but are more common in reproductive years and have an increased occurrence in menarchal females due to endogenous hormone production (Mobeen 2021). Simple ovarian cysts are common incidental findings in women ≥55 years of age because of the frequent use of high-resolution transvaginal ultrasound for ovarian cancer screening (Greenlee 2010). Hypo- and hyperthyroidism (autoimmune or not, as ovarian cyst is not considered a connective tissue disease) are risk

	factors, as well as obesity. Other risk factors include infertility treatment, tamoxifen, pregnancy, maternal gonadotropins, cigarette smoking, and tubal ligation. Patients treated with gonadotropins or other ovulation induction agents may develop cysts as part of ovarian hyperstimulation syndrome (Mobeen 2021).
Risk minimization measures	Routine risk minimization measures: Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: None.

Important Potential Risk: Pulmonary edema associated with PVOD	
Evidence for linking the risk to the medicine	Pulmonary edema following administration of pulmonary vasodilators used for the treatment of PAH could be due to previously unrecognized secondary angioproliferative processes caused by post-capillary obstruction, eg, PVOD, and/or due to combined pre-capillary and post-capillary pulmonary hypertension (Galiè 2015c, Galiè 2016, Opitz 2016). Pulmonary edema has been seen during clinical experience with other pulmonary vasodilators (endothelin receptor antagonists [ERAs], phosphodiesterase-5 inhibitors, riociguat, prostacyclin and its analogs). Fluid accumulation in the lungs has been reported with medicines that dilate blood vessels when used in patients with previously undiagnosed PVOD, which may be associated with PAH. There are no indications that macitentan is specifically implicated in this respect. However, should signs of fluid accumulation in the lungs occur when macitentan is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered.
Risk factors and risk groups	Patients with PVOD.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.4 ‘Special Warnings and Precautions for Use’ and PL section 2 ‘What you need to know before you take Opsumit’ Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: None.

Important Potential Risk: Testicular disorders and male infertility	
Evidence for linking the risk to the medicine	In animal studies, macitentan had small effects on the testicular function of male rats. The fertility of the animals was not affected. Decreases in sperm count have been observed in patients taking ERAs. Macitentan, like other ERAs, may have an adverse effect on spermatogenesis in men.
Risk factors and risk groups	Male patients.
Risk minimization measures	Routine risk minimization measures: SmPC section 4.6 'Fertility, pregnancy, and lactation' and PL section 2 'What you need to know before you take Opsumit' Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: None.

Missing Information: Pediatric patients	
Risk minimization measures	Routine risk minimization measures: SmPC sections 4.2 'Posology and method of administration' and PL section 2 'What you need to know before you take Opsumit' Legal status: medicinal product subject to restricted medical prescription Additional risk minimization measures: None.

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.