OrPha Swiss

# Summary of the Risk Management Plan (RMP)

for

# Treprostinil OrPha 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion (treprostinil)

RMP Version number 0.4
Data lock point 31-Dec-2018 – Date final 05-Dec-2019
MAH: OrPha Swiss GmbH, 8700 Küsnacht
Date: 04.01.2023

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 Treprostinil OrPha 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 Treprostinil OrPha in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. OrPha Swiss GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Treprostinil OrPha.

## Part VI: Summary of the risk management plan

# Summary of risk management plan for Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion (treprostinil)

This is a summary of the risk management plan (RMP) for Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion. The RMP details important risks of Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion, how these risks can be minimised, and how more information will be obtained about the medicinal product's risks and uncertainties (missing information).

Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the medicinal product should be used.

This summary of the RMP for Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion 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 Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion's RMP.

## I. The medicine and what it is used for

Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion is authorised for treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment (severity classified WHO Functional Class (FC) II, III or IV), to improve exercise capacity and symptoms of the disease (see SmPC for the full indication). It contains treprostinil as the active substance and it is given by continuous subcutaneous infusion via a subcutaneous catheter using an ambulatory infusion pump.

Further information about the evaluation of the medicinal product’s benefits can be found in Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage <*Pre-authorisation RMP (this line should be only edited by EMA):* link to the EPAR summary landing page. *Post-authorisation RMP (this line should be edited by the Applicant/MAH):* link to product’s EPAR summary landing page on the EMA webpage.>

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion, together with measures to minimise such risks and the proposed studies for learning more about the medicinal product's risks, 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 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, including PSUR 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 Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion. 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);

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | Hypotension |
| Important potential risks | Bleeding tendencies |
| Missing information | Use in patients with hepatic and / or renal impairment<br>Co-administration with CYP2C8 inhibitors/inducers |

## II.B Summary of important risks

| **Important identified risk: Hypotension** | |
|---|---|
| Evidence for linking the risk to the medicine | Common side effects reported in clinical studies associated with the use of treprostinil include infusion site pain and reaction, headache, diarrhoea, nausea, jaw pain, vasodilation, and hypotension [**Fehler! Verweisquelle konnte nicht gefunden werden.**, 2017]. |
| Risk factors and risk groups | Hypotension can affect people of all ages. However, people in certain age groups are more likely to have certain types of hypotension. Older adults are more likely to have orthostatic and postprandial hypotension. Children and young adults are more likely to have neurally mediated hypotension [**Fehler! Verweisquelle konnte nicht gefunden werden.**, 2018]. |

| **Important identified risk: Hypotension** | |
|---|---|
| | People who take certain medicines—such as diuretics or other antihypertensive medicines—are at increased risk for hypotension. Certain conditions also increase the risk for hypotension. Examples include central nervous system disorders (such as Parkinson's disease) and some heart conditions [**Fehler! Verweisquelle konnte nicht gefunden werden.**, 2018]. As stated in the current SmPC for the product, concomitant administration of Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion with diuretics, antihypertensive agents or other vasodilators.<br><br>Other risk factors for hypotension include being immobile for long periods, being out in the heat for a long time, and pregnancy. Hypotension during pregnancy is normal and usually disappears after birth [**Fehler! Verweisquelle konnte nicht gefunden werden.**, 2018].<br><br>Patients with systolic arterial pressure of less than 85 mmHg are at higher risk to develop systemic hypotension with the use of Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion. |
| Risk minimisation measures | Routine risk minimisation measures<br><br>SmPC section 4.8.<br><br>PL section 4.<br><br>The SmPC includes a warning in section 4.4 stating that in subjects presenting with low systemic arterial pressure, treprostinil treatment may increase the risk of systemic hypotension. Treatment is not recommended for patients with systolic arterial pressure of less than 85 mmHg. It is recommended to monitor systemic blood pressure and heart rate during any change in dose with instructions to stop the infusion if symptoms of hypotension develop, or a systolic blood pressure of 85 mmHg or lower is detected.<br><br>According to section 4.5 of the SmPC, concomitant administration of Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion with diuretics, antihypertensive agents or other vasodilators increases the risk of systemic hypotension.<br><br>Section 4.7 of the SmPC states that the initiation of treatment or dosage adjustments may be accompanied by undesirable effects such as symptomatic systemic hypotension or dizziness which may impair ability to drive and operate machinery.<br><br>In addition, section 4.9 states that symptoms of overdose include hypotension and that patient experiencing symptoms of overdose should, after consultation with their physician, immediately reduce their dose of treprostinil depending on the severity of the symptoms until the symptoms of overdose have resolved. Dosing should be recommenced with caution under |

| **Important identified risk: Hypotension** | |
|---|---|
| | medical control and patients monitored closely for recurrence of unwanted symptoms.<br>According to section 2 of the PL, patients must inform their doctor if their blood pressure decreases and/or if they are received or have recently received antihypertensive drugs or other vasodilators or diuretics.<br>In addition, this section of the PL includes that the use of product may induce low blood pressure with dizziness or fainting and that in such case patients must not drive or operate machinery.<br>According to section 3 of the PIL, if patients accidentally receive an overdose of the product they may experience events like low blood pressure (dizziness, light-headedness or fainting).<br>Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Special medical prescription.<br>Additional risk minimisation measures:<br>None. |

| **Important potential risk: Bleeding tendencies** | |
|---|---|
| Evidence for linking the risk to the medicine | Data obtained from clinical studies and published literature. Bleeding events as a side effect of treprostinil especially with concomitant use of anticoagulants is reported in the product information of Remodulin for PAH patients. However, in the clinical trial CTREPH 116-02, no bleeding event has been reported during the complete study period despite the wide use of anticoagulants in CTEPH patients (104 of 105 patients received at least one concomitant anticoagulant) [Study Report CTREPH 116-02]. |
| Risk factors and risk groups | Bleeding events can affect all patients receiving treprostinil therapy. This risk is expected to be higher for patients with concomitant anticoagulative therapy, which is common for CTEPH patients.<br>No other special patient groups (e.g. age group) are identified for which the risk of bleeding complications is higher than for others. |
| Risk minimisation measures | Routine risk communication:<br>SmPC sections 4.4, 4.5 and 4.8<br>PL section 2 and 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>None. |

| **Important potential risk: Bleeding tendencies** | |
|---|---|
| | Other routine risk minimisation measures beyond the Product Information:<br>Legal status: Special medical prescription |

| **Missing information:** | |
|---|---|
| **Risk** | **What is known** |
| **Use in patients with hepatic and / or renal impairment** | As metabolism of treprostinil is influenced by the functionality of both the liver and kidneys, the use in patients with hepatic and / or renal impairment is regarded as missing information. |
| **Co-administration with CYP2C8 inhibitors/inducers** | As metabolism of treprostinil is suspected to be influenced by the enzyme CYP2C8, co-administration with CYP2C8 inhibitors / inducers is regarded as missing information. |

## 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 Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion.

### *II.C.2 Other studies in post-authorisation development plan*

There are no studies required for Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion.