Remodulin®

Infusionslösung

Active substance: Treprostinil

Summary of the Risk Management Plan (RMP)

Based on EU-RMP V6.1
Version 1.0 (August 2022)
Marketing Authorisation Holder: Gebro Pharma AG, Liestal

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 "Remodulin" 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 "Remodulin" in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Name of the marketing authorisation holder" is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Remodulin".

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for REMODULIN (Treprostinil)

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

Remodulin's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Remodulin should be used.

I. The medicine and what it is used for

Remodulin is authorized for treatment of idiopathic or heritable PAH to improve exercise tolerance and symptoms of the disease in patients classified as NYHA FC class III (see SmPC for the full indication). It contains treprostinil as the active substance and it is given by solution for infusion in 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL via SC or IV routes.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Remodulin, together with measures to minimize such risks and the proposed studies for learning more about Remodulin'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 the case of Remodulin, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

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*.

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

II.A List of important risks and missing information

Important risks of Remodulin are risks that need special risk management activities to further investigate or minimize 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 Remodulin. 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	Risks attributable to Drug Delivery System: central venous catheter (CVC)-related bloodstream infections (BSIs)and sepsis (IV) Safety in patients with hepatic impairment Abrupt withdrawal or sudden large dose reduction Systemic hypotension
Important potential risks	Bleeding tendencies Co-administration with a CYP 2C8 inhibitor or inducer
Missing information	Safety of use in patients less than 18 years of age Effects of treprostinil infusion therapy on pregnancy, pregnancy outcome, labor and delivery, lactation

II.B Summary of important risks

Important identified risk: Central venous catheter (CVC) related bloodstream infections (BSIs)	
Evidence for linking the risk to the medicine	A CDC retrospective survey of seven centers in the United States that used IV Remodulin for the treatment of PAH found an incidence rate for catheter-related BSIs of 1.1 events per 1000 catheter days (CDC 2007).
Risk factors and risk groups	All patients with an indwelling CVC used for chronic, continuous administration of IV medication are at risk of developing catheter-related BSI. The level of risk varies between patients and is dependent on a number of factors, particularly the attention paid to scrupulous infection control procedures during manipulation of the medication reservoir and infusion delivery system.
Risk minimization measures	Routine risk minimization measures: *SmPC Section 4.2 provides advice on minimizing the risk of CVC-BSIs* *SmPC Section 4.4 indicates that the preferred method of drug delivery is via SC infusion based on the CVC-BSI risk.* Additional risk minimization measures: *General catheter care based on international catheter care guidelines for Remodulin and Flolan provided by the US Pulmonary Hypertension Association (Doran 2008)* *Recommendations include:*

	- *To protect the catheter and connecting device with an impermeable cover during a shower.* - *hand hygiene.* - *catheter hub instructions, including use of a closed-hub system and prostanoid reconstitution and administration guidelines* *Materials used to convey these recommendations include:* - *Slide lecture kit for doctors and nurses that presents CVC-related BSI risk minimization techniques and best practice recommendations* - *Patient brochure for patients started on IV administration* - *Dear Doctor Letter to be sent to all potential prescribers informing them of the risks* - *Patient Questionnaire on practicalities of CVC-related BSI prevention techniques* - *Events of Special Interest report form for doctors to complete in the event of them becoming aware of a CVC-related BSI.* - ***Fehler! Verweisquelle konnte nicht gefunden werden.***
Additional pharmacovigilance activities	Additional PV activities: *An assessment of risk minimization activities is undertaken every 6 months and reported in the PBRER.*
Important identified risk: Use in Patient's with Hepatic Impairment	
Evidence for linking the risk to the medicine	Remodulin SmPC Pharmacokinetic study in subjects with mild to moderate hepatic impairment for Remodulin (P02:01) Severe pulmonary hypertension in liver transplant candidates. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Liver Transpl Surg. 1997;3(5):494. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. Colle IO, Moreau R, Godinho E, Belghiti J, Ettori F, Cohen-Solal A, Mal H, Bernuau J, Marty J, Lebrec D, Valla D, Durand F. Hepatology. 2003;37(2):401.
Risk factors and risk groups	Patients with underlying hepatic dysfunction, Child-Pugh classes A and B.
Risk minimization measures	Routine risk minimization measures: *SmPC Section 4.2 advises caution when treating patients with mild to moderate hepatic impairment due to the risk of increased systemic exposure of treprostinil leading to an increase in dose-*

	dependent, prostanoid adverse effects. Section 4.2 also provides dosing guidance. *SmPC Section 4.3 states that Remodulin is contraindicated in patients with severe liver impairment (Child-Pugh Class C)* *Annex 4:* ***Fehler! Verweisquelle konnte nicht gefunden werden.***
Important identified risk: Abrupt withdrawal	
Evidence for linking the risk to the medicine	As stated in the Remodulin SmPC, abrupt withdrawal or sudden marked reductions in the dose of Remodulin may cause a rebound in PAH. It is therefore recommended that interruption of Remodulin therapy be avoided and that the infusion be re-started as soon as possible after an abrupt accidental dose reduction or interruption. This is also provided in the Remodulin EU PIL. The risk-benefit assessment of the IV external pump versus the LENUS pro® implantable pump describes 1 case involving a variation on the flow rate and associated with the external pump, whereas 23 cases have been identified for the implantable pump, including 11 cases of increased flow rate and 4 reduced residual volume (possibly reflecting an increased flow rate). Five (5) serious cases described an increased flow rate leading to overdose probably due to a pump defect, as considered by the reporter. One patient developed symptoms related to the overdose; cardiogenic shock and cardiac failure were developed in 2 patients, respectively; another patient developed right ventricular failure and respiratory failure; and the remaining patient did not report any other adverse event. In 3 cases, the pumps were described as being defective and were replaced by new ones.
Risk factors and risk groups	Abrupt withdrawal or sudden marked reductions in the dose of Remodulin may cause a rebound in PAH. Underdose, including and up to abrupt withdrawal, may occur due to device malfunction or human error. Device malfunctions could include infusion catheter kinking or occlusion, infusion device not working correctly and delivering the incorrect dose or depletion of the pump reservoir, thereby precipitating worsening or rebound PAH.
Risk minimization measures	Routine risk minimization measures: *SmPC Section 4.2 advises against interruption of Remodulin therapy due to rebound PAH and suggest restarting therapy as soon as possible after interruption.* *SmPC Section 4.2 has detailed recommendations regarding implantable pump alarm and filling procedure Full details on dosing calculations are provided in the manufacturer's device IFU manual (section 11).* **Implantable pump IFU Manual** 5.1 Warnings.

	Infusion pump may display an increase in infusion rate over the course of its use 5.2 Precautions Rapid decrease in flow rate is demonstrated when reservoir volume is less than 2 ml. Section 11.1.3 Reference Flow Rate and Section 11.2 Flow Rate Deviations The infusion pump may display an increase in infusion rate over the course of its use. Safe clinical use of the implanted pump is assured by comparing the actual flow rate as measured at each refill with the reference flow rate and adjusting the reference flow rate accordingly. Full details on dosing calculations are provided in the manufacturers pump IFU manual (Section 11). . *Annex 4:* **External or internal pump incidents or dysfunctions Targeted Follow-up Form**
Important identified risk: Systemic hypotension	
Evidence for linking the risk to the medicine	Final Remodulin clinical study report (P01:04 and P01:05). In controlled studies of SC Remodulin (P01:04/05), the frequency of hypotension was 4% in the Remodulin group compared with a frequency of 2% in the placebo group. The frequency of syncope was 3% in the Remodulin group compared to 5% in the placebo group. As discussed in the clinical study report, syncope is attributable to the progression of underlying PAH.
Risk factors and risk groups	Hypotension is likely related to right heart failure, but hypotension may also be temporarily aggravated by Remodulin dose increases (Piazza 2005; Harjola 2016). Hypotension in patients with PAH may be a result of either low cardiac output from right ventricular failure or reduced systemic vascular resistance from over vasodilation or infection (DeMarco 2005). Co-administration of anti-hypertensive medications and patients with baseline systemic hypotension are additional risk factors. Patients with systemic hypotension may present with syncopal episodes and depending on the degree of hypotension, may require hospitalization. "In the Systolic Blood Pressure Intervention Trial, patients at high cardiovascular risk who were already using antihypertensive drugs targeting a systolic BP of 120 mmHg had an approximately two-fold risk of syncope vs. the control group targeting a systolic BP of 140 mmHg" (Brignole 2018).
Risk minimization measures	Routine risk minimization measures: *SmPC Section 4.4 suggests monitoring systemic blood pressure specifically during dose titration increases.*

Important potential risk: Bleeding Tendencies	
Evidence for linking the risk to the medicine	Final Remodulin clinical study report (P01:04 and P01:05). Reported episodes of bleeding in the literature likely related to treprostinil have included hematoma (Vachiéry 2002) and bleeding at the SC infusion site (Lang 2006). Subdural hematoma (Tapson 2006) and haemoptysis (Sitbon 2007) was considered unrelated to treprostinil. It should also be noted that in the Tyvaso open-label experience, 3 serious episodes of haemoptysis (1 fatal) were reported (current Tyvaso PI). It is unclear to what degree haemoptysis resulted from inhalation of treprostinil, in particular, drug effect of treprostinil by any route, or underlying PH unrelated to therapy (LeVarge 2012). In clinical trials, 65 haemorrhagic events were reported as SAEs; 5 were deemed possibly/probably attributable to Remodulin.
Risk factors and risk groups	The incidence of bleeding events is increased in PAH patients (Opitz 2009). This applies particularly to PAH that is associated with connective tissue diseases, congenital heart disease, and chronic thromboembolic pulmonary hypertension. Patients taking concomitant medications that are anti-coagulants or inhibit platelet aggregation are at an increased risk of bleeding.
Risk minimization measures	Routine risk minimization measures: SmPC Section 4.3 states that Remodulin is contraindicated in patients with active bleeding conditions. SmPC Section 4.4 advises caution in situations with an increased risk of bleeding due to treprostinil's inhibition of platelet aggregation. SmPC Section 4.5 suggests close monitoring of patients taking concomitant anticoagulants due to an increase in the risk of bleeding.
Important potential risk: Co-administration with a CYP 2C8 inhibitor or inducer	
Evidence for linking the risk to the medicine	Final Report Amendment for ABC Laboratories Study No. 49252: An Investigation of the Inhibitory Potential of UT-15C towards Human Hepatic Microsomal Cytochrome P450 Isoforms.
Risk factors and risk groups	Patient's adding or subtracting a CYP 2C8 inhibitor or inducer to their treatment regimen.
Risk minimization measures	Routine risk minimization measures: *SmPC Sections 4.4 and 4.5 advise that administration of treprostinil with an inhibitor or inducer can cause an increase or decrease in exposure, respectively, and that a dose reduction (inhibitor) or increase (inducer) should be considered.*
Missing information: Safety of use in patients <18 years old	
Risk minimization measures	No risk minimization measures

Additional pharmacovigilance activities	Additional PV activities: Study 3 of Paediatric Investigation Plan, category 3 - Intravenous Remodulin (Treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study. (Protocol: RIV-PN-201). See Section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Safety of use in pregnancy, labor, delivery and lactation	
Risk minimization measures	Routine risk minimization measures: *SmPC Section 4.6 suggests Remodulin should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the foetus.*

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

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

II.C.2 Other studies in post-authorization development plan

Study short name

Intravenous Remodulin (Treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study. (Protocol: RIV-PN-201)

Purpose of the study:

To explore the safety and efficacy of IV Remodulin as add-on therapy in neonatal subjects with PPHN as compared to placebo.

To evaluate PK.