Part VI: Summary of the risk management plan

Summary of risk management plan for Treprostinil beta Infusionslösung (treprostinil)

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

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

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

I. The medicine and what it is used for

Treprostinil beta is authorised is authorised to treat idiopathic or heritable pulmonary arterial hypertension (PAH) in patients with moderate severity of the symptoms. Pulmonary arterial hypertension is a condition where your blood pressure is too high in the blood vessels between the heart and the lungs, causing shortness of breath, dizziness, tiredness, fainting, palpitations or abnormal heartbeat, dry cough, chest pain and swollen ankles or legs.

Treprostinil beta contains treprostinil as the active substance and it is given as an infusion, either under the skin (subcutaneously) or into a blood vessel (intravenously).

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

Important risks of Treprostinil beta, together with measures to minimise such risks and the proposed studies for learning more about Treprostinil beta'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 Treprostinil beta, 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 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 Treprostinil beta is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Treprostinil beta 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 beta. 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	• Systemic hypotension • Central venous catheter related blood stream infections and sepsis associated with the intravenous route of administration (risks attributable to drug delivery system) • Rebound in pulmonary hypertension due to abrupt withdrawal or sudden large dose reduction
Important potential risks	• None
Missing information	• Safety in pregnancy and breastfeeding • Safety in patients less than 18 years of age

II.B Summary of important risks

Important identified risk: Systemic hypotension	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.4, 4.5, 4.7, 4.8, 4.9* *PL section 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Advice to reduce the infusion rate to diminish their intensity in case hypotension persists or becomes intolerable to the patient is included in SmPC section 4.2.* *Recommendation 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*

Important identified risk: Systemic hypotension	
	mmHg or lower is detected is included in SmPC section 4.4 *Advice not to drive or operate machinery in case of dizziness or fainting is included in SmPC section 4.7 and PL section 2.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Important identified risk: Central venous catheter-related blood stream infections and sepsis associated with the intravenous route of administration (risks attributable to drug delivery system)	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2, 4.4, 4.8, 6.3* *PL section 2, 3, 4* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Subcutaneous infusion (undiluted) is the preferred mode. Continuous intravenous infusion should be reserved for those patients that are stabilised on a subcutaneous infusion and become intolerant of it and in whom the risks of an indwelling central venous catheter are considered acceptable. This information is included in SmPC section 4.2* *For patients that require treatment with a continuous intravenous infusion of treprostinil delivered via an in-dwelling central venous catheter the risk of blood stream infection and sepsis can be minimised by adopting best practice guidelines and information on consideration of information on use as described in SmPC section 4.2 (e.g. duration of use of diluted treprostinil solution, use of in-line 0.2 micron filter, sse of a split septum closed hub system, infusion system luer lock inter-connections)* *Advice for patients to consult a doctor if fever develops whilst receiving intravenous treprostinil or the intravenous infusion site becomes red, swollen and / or*

Important identified risk: Central venous catheter-related blood stream infections and sepsis associated with the intravenous route of administration (risks attributable to drug delivery system)	
	painful to the touch, as this could be a sign of infection is included in PL section 2. Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* *Events of special interest form* Additional risk minimisation measures: *Healthcare professional training slides* *Patient questionnaire* *Patient brochure*

Important identified risk: Rebound in pulmonary hypertension due to abrupt withdrawal or sudden large dose reduction	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2, 4.4* *PL section 3* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation to avoid interruption of treprostinil therapy and to re-started the infusion as soon as possible after an abrupt accidental dose reduction or interruption is included SmPC section 4.2. The optimal strategy for reintroducing treprostinil infusion needs to be determined on a case by case basis by medically qualified personnel. In most cases, after an interruption of a few hours, restarting of treprostinil infusion can be done using the same dose rate; interruptions for longer periods may require the dose of treprostinil to be re-titrated.* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Safety in pregnancy and breastfeeding	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.6* *PL section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Advice to use treprostinil during pregnancy only if the potential benefit to the mother justifies the potential risk to the foetus and to discontinue breastfeeding is included in SmPC section 4.6* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *None*

Missing information: Safety in patients less than 18 years of age	
Risk minimisation measures	Routine risk minimisation measures *SmPC section 4.2* *PL section 3* Routine risk minimisation activities recommending specific clinical measures to address the risk: *None* Other routine risk minimisation measures beyond the Product Information: *Prescription-only medicine* Additional risk minimisation measures: *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 Treprostinil beta Infusionslösung.

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

There are no studies required for Treprostinil beta Infusionslösung.