EU Risk Management Plan
for
Trepulmix 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion (treprostinil)

RMP version to be assessed as part of this application:

RMP Version number:	V2.0
Data lock point for this RMP:	12-Jan-2023
Date of final sign-off:	12-Sep-2023
Rationale for submitting an updated RMP:	PRAC request for risk harmonisation (Treprostinil PSUR assessment EMEA/H/C/PSUSA/00003013/202205)
Summary of significant changes in this RMP:	PRAC request for update of safety concerns (Treprostinil PSUR assessment EMEA/H/C/PSUSA/00003013/202205) Removal of: - Important identified risk "hypotension" - Important potential risk "bleeding tendencies" - Missing information "Use in patients with hepatic and/or renal impairment" - Missing information "Co-administration with CYP2C8 inhibitors/inducers" Update of Epidemiology section

Other RMP versions under evaluation:

RMP Version number:	N/A
Submitted on:	N/A
Procedure:	N/A

Details of the currently approved RMP:

Version number:	V0.4
Approved with procedure:	EMEA/H/C/005207/0000
Date of approval (opinion date):	03-Apr-2020

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Part I: Product(s) Overview

Table 1 Part I.1 – Product Overview

Active substance(s) (INN or common name)	Treprostinil
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group: Antithrombotic agents; platelet aggregation inhibitors excl. heparin ATC code: B01AC21
Marketing Authorisation Applicant	SciPharm Sàrl
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Trepulmix 1 mg/ml solution for infusion Trepulmix 2.5 mg/ml solution for infusion Trepulmix 5 mg/ml solution for infusion Trepulmix 10 mg/ml solution for infusion
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Prostacyclin analogue.
	Summary of mode of action: It exerts a direct vasodilation effect on the pulmonary and systemic arterial circulation and, inhibits platelet aggregation.
	Important information about its composition: None.
Hyperlink to the Product Information	Please refer to eCTD Module 1.3.1 SmPC, Labelling and Package Leaflet
Indication(s) in the EEA	Current: Treatment of adult patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or persistent or recurrent CTEPH after surgical treatment (WHO Functional Class (FC) III or IV), to improve exercise capacity and symptoms of the disease.
	Proposed: Not applicable.
Dosage in the EEA	Current: The recommended initial infusion rate is 1.25 ng/kg/min. The infusion rate should be increased under medical supervision in increments of up to 1.25 ng/kg/min per week for the first four weeks of treatment and then up to 2.5 ng/kg/min per week. The dose should be adjusted on an individual basis and under medical supervision in order to achieve a maintenance dose at which symptoms improve and which is tolerated by the patient. During follow-up phases of clinical trials in pulmonary arterial hypertension (PAH) patients the mean doses reached after 12 months were 26 ng/kg/min, after 24 months were 36 ng/kg/min, and after 48 months were 42 ng/kg/min. Treprostinil 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion is administered undiluted by continuous subcutaneous infusion via a subcutaneous catheter using an ambulatory infusion pump.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Trepulmix 1 mg/ml solution for infusion: Each ml contains 1 mg treprostinil, as treprostinil sodium.

	Each 10 ml vial of solution contains 10 mg treprostinil as treprostinil sodium (sodium salt formed *in situ* during manufacture of the finished product). Trepulmix 2.5 mg/ml solution for infusion: Each ml contains 2.5 mg treprostinil, as treprostinil sodium. Each 10 ml vial of solution contains 25 mg treprostinil as treprostinil sodium (sodium salt formed *in situ* during manufacture of the finished product). Trepulmix 5 mg/ml solution for infusion: Each ml contains 5 mg treprostinil, as treprostinil sodium. Each 10 ml vial of solution contains 50 mg treprostinil as treprostinil sodium (sodium salt formed *in situ* during manufacture of the finished product). Trepulmix 10 mg/ml solution for infusion: Each ml contains 10 mg treprostinil, as treprostinil sodium. Each 10 ml vial of solution contains 100 mg treprostinil as treprostinil sodium (sodium salt formed *in situ* during manufacture of the finished product).
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Chronic thromboembolic pulmonary hypertension (CTEPH)

CTEPH is a progressive pulmonary vascular disorder, classified as group 4 pulmonary hypertension (PH) in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines - PH associated with pulmonary artery obstructions [Humbert et al, 2022]. The disease is usually a result of one or more episodes of pulmonary embolism and has been reported to occur in 0.6–4.4% of patients who have had a pulmonary embolism. CTEPH is characterised by macroscopic thromboembolic lesions within proximal or distal pulmonary arteries and microscopic pulmonary vasculopathy. The clinical consequences of these pathological changes, which can include intimal thickening, vascular remodelling and plexiform lesions, are elevated pulmonary vascular pressures and increased pulmonary vascular resistance (PVR), which can lead to right heart failure and death [Madani, 2017].

Incidence and prevalence:

The exact incidence of CTEPH has been difficult to discern. Current estimates are based either on the prevalence of patients with CTEPH referred to specialized pulmonary arterial hypertension centers or on small registries which follow patients prospectively after acute pulmonary embolism to identify incidence cases of CTEPH. Published estimates of the incidence of CTEPH vary widely due to differences in referral patterns and screening strategies after acute pulmonary embolism, in addition to the difficulties inherent to diagnostic confirmation of the disease [Fernandes, 2018]. Defining the true prevalence of CTEPH is also complicated by the presumed misdiagnosis of the disease because of nonspecific symptoms and the underuse of recommended tests available in guidelines [Delcroix, 2016].

According to Orphanet, the estimated incidence is ranging from 1/20,000-33,000 in the USA and Europe. It is also stated that the true prevalence of CTEPH is unknown; it is a rare disease but there are reports suggesting that it is underdiagnosed [Orphanet, 2021].

According to the analysis performed by Delcroix et al., some information on the disease burden can be derived from registries: (1) CTEPH represents at least 19% of patients currently referred to general pulmonary hypertension centers, (2) CTEPH incidence is approaching 5 per million inhabitants per year; and (3) its prevalence could reach 38.4 per million inhabitants [Delcroix, 2016].

The number of patients diagnosed with CTEPH is increasing, probably due to a deeper understanding of the disease and more active screening of patients after pulmonary embolism. By most estimates, CTEPH is a rare disease which occurs with an estimated incidence of 3–6 and prevalence of 26-38 cases per million adults [Leber et al, 2021; Delcroix et al, 2020; Kramm et al, 2018]. Published studies which actively surveyed patients after acute pulmonary embolism for the development of CTEPH found an incidence between 0.1 and 8.8% within two years of diagnosis [Fernandes, 2018].

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Registry data suggest that the prevalence of CTEPH is approximately equal in men and women, with an average age of onset in the sixth decade of life [Medrek, 2016]. The median age of CTEPH patients at diagnosis is 63 years and both genders are equally affected; paediatric cases are extremely rare [Galiè, 2016]. Specifically, an international registry of 362 patients under the age of 18 with confirmed PH found

that the majority of cases were attributed to PAH (88%) and only 0.8% cases were attributable to CTEPH [Berger, 2011].

Many risk factors for the development of CTEPH have been identified. Given the now-accepted thromboembolic hypothesis of the disease, it is perhaps unsurprising that having a prior thromboembolic event is a risk factor for the development of this condition. Although a subset of patients eventually diagnosed with CTEPH have no history of thromboembolic disease, older data suggests that these patients comprise a relative minority [Medrek, 2016].

The thromboembolic nature of CTEPH and the association between pulmonary embolism and/or deep vein thrombosis have been well established. The Japanese registry revealed a history of deep vein thrombosis and acute pulmonary embolism in 50.4% and 37.2%, respectively. The corresponding percentages were 56.1% and 74.8% in the large European database and 49.2% and 70.6% in the California-San Diego Pulmonary Endarterectomy registry [Bazmpani, 2017].

Numerous acquired and inherited coagulopathies have been linked to the development of CTEPH. In the study conducted by Bazmpani et al. 41% of population reported at least one thrombophilic disorder [Bazmpani, 2017]. Hypercoagulable states that have shown to confer a higher risk of CTEPH development include elevated factor VIII levels, lupus anticoagulant/antiphospholipid antibodies and factor V Leiden mutations [Medrek, 2016].

An elevated level of factor VIII was identified as a risk factor for CTEPH in a study of 122 patients compared with 82 healthy controls and 88 patients with PAH ($p<0.0001$ for both). This was confirmed in a recent comparison of factor VIII levels in 45 patients with CTEPH versus 200 patients with non-thromboembolic PH ($p<0.01$). Von Willebrand factor was also elevated in these patients compared with patients in the control group ($p<0.009$) [Kim, 2012].

Elevated expression of type 1 plasminogen activator inhibitor (PAI-1) has been found in neovessels within CTEPH thrombi, which may affect clearance of the thrombus. However, when PAI-1 was measured in plasma from patients with CTEPH, no difference was seen in the relative levels of plasminogen activator and PAI-1 compared with healthy controls, which may suggest that any changes in PAI-1 expression remain localised to the CTEPH thrombus [Kim, 2012].

Abnormalities in fibrinogen structure and function have also been observed in patients with CTEPH. In vitro studies have shown that fibrinogen from patients with CTEPH is more resistant to fibrinolysis than that from healthy controls. Five fibrinogen variants have been identified in 33 patients with CTEPH. A significant association has also been seen between heterozygous fibrinogen Thr312Ala and CTEPH in 214 patients with CTEPH versus 200 healthy controls ($p<0.02$). Interestingly, the exposure of endothelial cells to fibrin and fibrinogen was shown to increase the activation of the cells by thrombin suggesting that this process may have a role in vascular remodelling [Kim, 2012].

CTEPH may also be more common in people with non-O blood groups. In one study, 77% of patients with CTEPH were found to have non-O blood groups compared with 58% of patients with PAH ($p<0.003$). This was later confirmed by the same group (OR 2.09, 95% CI 1.12–3.94; $p<0.019$) [Kim, 2012].

Elevated plasma levels of lipoprotein(a) may also contribute to a hypercoagulable state and were found to be significantly raised in patients with CTEPH compared with patients with PAH ($p<0.002$) and healthy controls ($p<0.0002$) [Kim, 2012].

Patients who have undergone a splenectomy have a significantly higher risk of developing CTEPH. In one study, 5.5% of patients with CTEPH had undergone a previous splenectomy compared with none in the

non-thromboembolic PH group (p<0.05). This supported an earlier finding that 8.6% of patients with CTEPH had a history of splenectomy compared with 2.5% of patients with idiopathic PAH and 0.6% of healthy controls (p<0.01 for both). Association between splenectomy and CTEPH was further supported in a study where 9% of patients with CTEPH had undergone a previous splenectomy compared with 0.5% of patients who had an acute pulmonary embolism (PE) but did not go on to develop PH (OR 13, 95% CI 2.7–127). The association between splenectomy and CTEPH may be due to the presence of abnormal erythrocytes that would normally be filtered out of the blood by the spleen. The abnormal expression of phosphatidylserine on the surface of erythrocytes may trigger the coagulation process, resulting in the formation of thromboembolic material. Reactive thrombocytosis may also be responsible for the increased risk of CTEPH following a splenectomy. Thrombocytosis occurs in 75% of patients following splenectomy and can lead to a hypercoagulable state and thrombosis. However, thrombocytosis was not found to be significantly associated with an increased risk of CTEPH (p<0.53), although it should be noted that only one patient in the control group of that study had a history of splenectomy [Kim, 2012].

Having foreign structures implanted in the heart also appears to increase the risk of CTEPH. In a number of studies, the presence of ventriculoatrial (VA) shunts for the treatment of hydrocephalus has been shown to increase the chance of developing this condition. The presence of pacemaker wires also increases risk [Medrek, 2016]. In one study, 2.8% of patients with CTEPH had a VA shunt compared with none of the patients with non-thromboembolic PH (p<0.05). In addition, 0.9% of patients with CTEPH had an infected pacemaker compared with none of the control group; however, this did not reach statistical significance. Similar results were observed in another study where 6% of patients with CTEPH had a VA shunt compared with 0.5% of patients with acute PE who did not subsequently develop PH (OR 13, 95% CI 2.5–129) [Kim, 2012].

It is hypothesized that superimposed infection of these exogenous structures could contribute to the delayed resolution of thromboemboli within the pulmonary vascular bed [Medrek, 2016].

Certain medical conditions characterized by high levels of inflammation have been linked to CTEPH. Specifically, inflammatory bowel disease and osteomyelitis have been found to increase the odds of developing this condition [Medrek, 2016]. One study found that 10% of patients with CTEPH had a chronic inflammatory condition compared with none of the patients who had not developed CTEPH following a PE (OR 67, 95% CI 7.9–8,832). A later study by the same group failed to show a statistically significant link between inflammatory conditions and an increased risk of CTEPH, although there were numerically more cases of inflammatory bowel disease amongst patients with CTEPH than amongst those with non-thromboembolic PH (12 versus three, respectively) [Kim, 2012] The link between inflammatory conditions and non-resolution of thrombotic disease is supported by data suggesting that inflammatory markers are high in patients with CTEPH compared to controls [Medrek, 2016].

History of malignancy confers an increased risk of developing this condition, as does being on thyroid hormone replacement, although it is unclear if this is due to the possible prothrombotic characteristics associated with the hypothyroid state or a direct effect of the thyroid hormone replacement [Medrek, 2016; Kim, 2012].

While traditionally there were no known familial or genetic links in CTEPH, some recent studies have suggested that a genetic predisposition could be present. One case of familial CTEPH has been reported, and BMPR2 mutations have been found in patients with CTEPH. A recent Chinese study found that patients with CTEPH had a higher frequency of mutations in the known PAH-related genes. Although these results are preliminary, they offer insight into the pathophysiology of this disease [Medrek, 2016].

The main existing treatment options:

The standard of care in CTEPH is the surgical removal of thromboembolic material from the larger vessels using pulmonary endarterectomy (also known as pulmonary thromboendarterectomy). This provides major clinical and haemodynamic improvements and is associated with increased survival. However, this procedure is invasive and can pose too high a risk to some patients. Furthermore, depending on the nature and location of the thrombi, and the extent of the underlying microvasculopathy, not all patients are candidates for surgery. An emerging catheter-based interventional technique, called balloon pulmonary angioplasty (BPA) or percutaneous transluminal pulmonary angioplasty, is an alternative management option for some patients, who may, for example, have lesions too distal to be treated by pulmonary endarterectomy. CTEPH patients may also benefit from medical therapies that target the underlying microvascular disease [Madani, 2017].

In parallel to the progress made in interventional and surgical techniques in recent years, advances have also been made in the field of medical therapy to target microvascular disease in patients with inoperable CTEPH. There is a rationale for using medical therapies that are typically used in pulmonary PAH to treat patients with inoperable CTEPH, based on observations that PAH and CTEPH share similar histopathological changes. Currently, beside Trepulmix only one pharmacological therapy is licensed for the treatment of CTEPH, the soluble guanylate cyclase stimulator riociguat. Riociguat is approved for adults with inoperable CTEPH or those who have persistent or recurrent CTEPH following surgical treatment, and its use is recommended in the ESC/ERS guidelines [Humbert et al, 2022].

Endothelin receptor antagonists and phosphodiesterase type 5 inhibitors are not currently approved for use in CTEPH, but are commonly used in clinical practice, both in inoperable patients and those with recurrent or persistent PH after surgery [Humbert et al, 2022].

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

CTEPH patients, if left untreated, have a poor prognosis: survival rates at 5 years have been reported at 30% for patients with mean pulmonary arterial pressure (mPAP) >40 mmHg, and 10% for patients with an mPAP >50 mmHg [Madani, 2017; Gopalan, 2017].

Important co-morbidities:

A number of comorbidities are present in patients with CTEPH. In the population of the study conducted by Bazmpani et al., a high percentage of obesity, systemic hypertension, and noninsulin diabetes mellitus was observed, highlighting that traditional cardiovascular risk factors should not be overlooked in these patients [Bazmpani, 2017].

Part II: Module SII - Non-clinical part of the safety specification

Not applicable.

Part II: Module SIII - Clinical trial exposure

Treprostinil is a well-known synthetic prostacyclin analogue authorised in the EU since 2002 under the trade name Remodulin (originator: Ferrer Internacional, S.A., European birth date: May 2002). Remodulin is marketed as a 1.0, 2.5, 5.0 or 10.0 mg/ml solution for infusion for the treatment of a pulmonary hypertension (PH) subtype called pulmonary arterial hypertension (PAH). Specifically, the indication for Remodulin is listed as: idiopathic or heritable PAH to improve exercise tolerance and symptoms of the disease in patients classified as New York Heart Association (NYHA) functional class III.

Trepulmix (treprostinil) was developed by SciPharm Sàrl and is marketed as a 1.0, 2.5, 5.0 or 10.0 mg/ml solution for infusion with a comparable formulation as the originator. Trepulmix is indicated for the treatment of adult patients with WHO Functional Class (FC) III or IV and:
- inoperable chronic thromboembolic pulmonary hypertension (CTEPH), or
- persistent or recurrent CTEPH after surgical treatment to improve exercise capacity.

Clinical Study CTREPH 116-02 (EudraCT No.: 2008-006441-10)

Title: A double blind controlled clinical study to investigate the efficacy and tolerability of subcutaneous Treprostinil sodium in patients with severe non-operable Chronic Thromboembolic Pulmonary Hypertension (CTREPH II).

In this randomised, multi-site (Austria, Czech Republic, Germany, Poland), comparator-controlled clinical trial, a total of 105 male (53.3%) and female (46.7%) adult patients with inoperable CTEPH or persistent or recurrent CTEPH after PEA (18-88 years of age) were divided into two treprostinil treatment groups (53 high dose and 52 low dose patients, treated with SC infusion for a total of 24 weeks) as follows. In the high dose group, patients were administered an SC dose via infusion pump that increased from approximately 1 to a target dose of approximately 30 ng/kg/min for the first 12 weeks, followed by 12 weeks of stable perfusion; in the low dose group, the target dose was approximately 3 ng/kg/min following the same schedule. The demographics of the two patient populations is listed in the section below (see Table 7). This dose was selected based on the previous results of (Lang et al., 2006), showing the efficacy of doses of ≤ 40 ng/kg/min at 36 months of treatment, and is also in line with recommendations for the use of treprostinil in the treatment of PAH.

Table 2 SIII.1: Gender

	High dose (N = 53)		Low dose (N = 52)		Total (N = 105)	
	N	%	N	%	N	%
male	34	64.2	22	42.3	56	53.3
female	19	35.8	30	57.7	49	46.7
Total	53	50.5	52	49.5	105	100.0

Table 3 SIII.2: Ethnicity

	High dose (N = 53)		Low dose (N = 52)		Total (N = 105)	
	N	%	N	%	N	%
Caucasian	52	98.1	22	42.3	56	53.3
Iran middle	1	1.9	30	57.7	49	46.7
Total	53	50.5	52	49.5	105	100.0

Table 4 SIII.3: Other demographics

Patient demographic	High dose (N = 53)	Low dose (N = 52)	Total (N = 105)
Mean age in y (range)	68.06 ± 11.16 (30 – 88)	60.58 ± 14.59 (18 – 82)	64.35 ± 13.44 (18 – 88)
Mean weight in kg (range)	76.94 ± 15.17 (46 – 133)	80.42 ± 16.99 (45 – 130)	78.66 ± 16.11 (45 – 133)
Mean height in cm (range)	168.72 ± 9.26 (152 – 190)	168.31 ± 9.30 (148 – 187)	168.51 ± 9.24 (148 – 190)

Part II: Module SIV - Populations not studied in clinical trials

Not applicable.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Calculated exposure in post-authorisation setting was based on defined daily dose (DDD) of 4.3 mg according to the WHO Collaborating Centre for Drug Statistics Methodology.

An estimate of the number of Daily Doses of Treprostinil during the reporting period was calculated from the sales volumes according to the following formula:

$$Number\ of\ Daily\ Doses\ = \frac{\text{Total quantity of Treprostinil sold (mg)}}{DDD\ (mg)}$$

The total quantity of Treprostinil sold (in mg) was determined by multiplying the number of units (vials) by the quantity (mg) of Treprostinil in the unit (strength of the formulation multiplied by the number of mL per vial) and summing the totals. Note that no data was available regarding age and/or sex of the exposed patients, or exposure in risk populations (e.g., patients with renal or hepatic impairment).

To estimate patient-years, the number of Daily Doses has to be divided by 365:

$$Patient - years\ = \frac{Number\ of\ Daily\ Doses}{365\ days}$$

SV.1.2 Exposure

Calculation is based on the method described in section SV1.1 Method used to calculate exposure.

Cumulatively at the Data lock point (DLP) of the Treprostinil PSUR 03 (reporting period 22-May-2021 – 21-May-2022), the total quantity of treprostinil sold was 83,655 mg, corresponding to 19,454.65 Daily Doses (53.30 patient-years).

Table 5 SV.1.2 Trepulmix® (treprostinil) sales volume worldwide to the date 21-May-2022

Country	Product	Units Sold [vials]	Total mg	Patient years [DDD 4.3 mg]
Germany	Trepulmix	[redacted]		
Spain	Trepulmix			
Ireland	Trepulmix			
Croatia	Trepulmix			
Lithuania	Trepulmix			
Latvia	Trepulmix			
Poland	Trepulmix			
Slovenia	Trepulmix			
Total		**1433**	**83,655**	**53.30**

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Headache
- Dizziness
- Vasodilatation
- Diarrhoea
- Nausea
- Rash
- Pruritus
- Jaw pain
- Myalgia
- Arthralgia
- Infusion site pain, infusion site reaction, bleeding or haematoma
- Oedema
- Bone pain

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Generalized rashes, sometimes macular or papular in nature, and cellulitis

Known risks that require no further characterisation and are followed up via routine pharmacovigilance activities namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Medication errors, including due to wrong handling of the pumps

The potential for medication errors is not rated as high risk during the therapy with treprostinil. Beside the thorough training of all patients, patients will not be given different strengths of the product for self-administration but only one strength. In addition, the different strengths are designed in a way that they can easily be distinguished by colours with matching coloured flip-off caps.

In addition, even in case of a 10-fold overdose the resulting symptoms are relatively quick reversible. The main source of potential risks for application of treprostinil s.c. is the choice and handling of a suitable infusion pump. It is of utmost importance to ensure that healthcare professionals and patients are trained well to avoid medication errors due to wrong handling of the pump.

Country specific training plans will be elaborated and implemented together with the clinical centres and the provider of the infusion pump before the launch of the product in the respective member state. The applicant will ensure together with supported infusion pump providers the establishment of a service hotline for the handling of the respective infusion pump.

Routine pharmacovigilance activities including a routine PSUR preparation and the proposed warnings and precautions in the proposed product information texts are regarded to be sufficient as risk minimisation measures for medication errors.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk 1: Hypotension

Treprostinil is a potent pulmonary and systemic vasodilator and, therefore, in subjects presenting with low systemic arterial pressure, treprostinil treatment may increase the risk of systemic hypotension.

Risk-benefit impact:

Excessive hypotension can lead to severe conditions as circulatory collapse.

However, hypotension associated with the use of treprostinil is usually mild and transient.

Important Potential Risk 1: Bleeding tendencies

Considering the antiplatelet effect of treprostinil and the need for anticoagulative therapy of CTEPH patients, bleeding tendencies are theoretically a risk for CTEPH patients. As no bleeding event has been reported in the clinical trial CTREPH 116-02 in CTEPH patients, bleeding tendencies is classified as important potential risk.

Missing Information 1: 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.

Missing Information 2: 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

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns are proposed with this update.

No reclassification of safety concerns is proposed with this update.

Removal of safety concerns is proposed following PRAC recommendations in the Treprostinil PSUR assessment EMEA/H/C/PSUSA/00003013/202205, dated 12-Jan-2023:

"Based on the review of the current PSUR data, it is concluded by the PRAC that several safety concerns are no longer considered important (i.e., not likely to have an impact on the B/R), and can therefore be removed:

- *from the RMP of Trepulmix (SciPharm Sàrl): important identified risk Hypotension; important potential risk Bleeding tendencies and missing information Use in patients with hepatic and/or renal impairment and Co-administration with CYP2C8 inhibitors/inducers;"*

Therefore, the removal of the following safety concerns is proposed:

- Important identified risk "Hypotension"
- Important potential risk "Bleeding tendencies"
- Missing information "Use in patients with hepatic and/or renal impairment"
- Missing information "Co-administration with CYP2C8 inhibitors/inducers"

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

For the current update, no important identified risks or important potential risks remain to be presented.

SVII.3.2. Presentation of the Missing Information

For the current update, no missing information remains to be presented.

Part II: Module SVIII - Summary of the safety concerns

Table 6 SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	none
Important potential risks	none
Missing information	none

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are carried out for all safety concerns and consist of

- Identification of any report of the addressed safety concerns in clinical practice
- Collection of safety data from the published case reports, clinical studies, reviews or other publications
- Periodic review in PSURs / PBRERs

Other routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

None.

III.2 Additional pharmacovigilance activities

No additional pharmacovigilance activities will be conducted.

III.3 Summary Table of additional Pharmacovigilance activities

No ongoing or planned categories 1-3 safety studies have been conducted.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are planned at this stage by the MAH.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 7 Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
none	not applicable
Important potential risks	
none	not applicable
Missing information	
none	not applicable

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimisation Measures

Table 8 Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
none	not applicable	not applicable

Part VI: Summary of the risk management plan

Summary of risk management plan for Trepulmix 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 Trepulmix 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion. The RMP details important risks of Trepulmix 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).

Trepulmix 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 Trepulmix 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, or any changes to the current safety concerns will be included in updates of the RMP for Trepulmix 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion.

I. The medicine and what it is used for

Trepulmix 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) III or IV), to improve exercise capacity and symptoms of the disease (see SmPC for the full indication). It contains treprostinil as active substance and 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 Trepulmix 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.

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

Important risks of Trepulmix 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 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 Trepulmix 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 Trepulmix 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	none
Important potential risks	none
Missing information	none

II.B Summary of important risks

No important identified risks, important potential risks or missing information are identified for Trepulmix 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion (see II.A List of important risks and 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 Trepulmix 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 Trepulmix 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml solution for infusion.

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.