ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Trepulmix 1 mg/ml solution for infusion

One ml of solution contains 1 mg treprostinil (as sodium salt).
Each 10 ml vial of solution contains 10 mg treprostinil (as sodium salt).

Excipient with known effect
Each 10 ml vial contains 36.8 mg (1.60 mmol) sodium.

Trepulmix 2.5 mg/ml solution for infusion

One ml of solution contains 2.5 mg treprostinil (as sodium salt).
Each 10 ml vial of solution contains 25 mg treprostinil (as sodium salt).

Excipient with known effect
Each 10 ml vial contains 37.3 mg (1.62 mmol) sodium.

Trepulmix 5 mg/ml solution for infusion

One ml of solution contains 5 mg treprostinil (as sodium salt).
Each 10 ml vial of solution contains 50 mg treprostinil (as sodium salt).

Excipient with known effect
Each 10 ml vial contains 39.1 mg (1.70 mmol) sodium.

Trepulmix 10 mg/ml solution for infusion

One ml of solution contains 10 mg treprostinil (as sodium salt).
Each 10 ml vial of solution contains 100 mg treprostinil (as sodium salt).

Excipient with known effect
Each 10 ml vial contains 37.4 mg (1.63 mmol) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear colourless to slightly yellow solution, free from visible particles with a pH of 6.0 – 7.2 and an osmolality between 253 and 284 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment with Trepulmix should be initiated and monitored only by clinicians experienced in the treatment of pulmonary hypertension. Treatment should be initiated under close medical supervision in a medical setting able to provide intensive care.

Posology

The recommended initial infusion rate is 1.25 ng/kg/min. If this initial dose is poorly tolerated, the infusion rate should be reduced to 0.625 ng/kg/min.

Dose adjustments
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 the follow-up phase of a clinical trial in CTEPH patients, the mean doses reached after 12 months were 31 ng/kg/min, after 24 months 33 ng/kg/min, and after 48 months 39 ng/kg/min. The respective maximum doses observed in the clinical trial were 52 ng/kg/min, 54 ng/kg/min and 50 ng/kg/min respectively.

Abrupt withdrawal or sudden marked reductions in the dose of treprostinil may cause a rebound of symptoms of chronic thromboembolic pulmonary hypertension. It is therefore recommended that interruption of treprostinil therapy is avoided and that the infusion is re-started as soon as possible after an abrupt accidental dose reduction or interruption. 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 up to 4 hours, restarting of treprostinil infusion can be done using the same dose rate; interruptions for up to 24 hours may require a dose reduction of up to 50% of the most recent dose with a subsequent uptitration to the clinically effective dose. Longer periods of interruption may require the dose of treprostinil to be re-titrated from even lower flow rates. In any case, the reintroduction of treprostinil should be under medical supervision.

Special populations

Hepatic impairment
The initial dose of Trepulmix should be decreased to 0.625 ng/kg/min and incremental dose increases should be made cautiously (see section 5.2). Increments could be reduced to 0.625 ng/kg/min per dose increase, the final decision on the dose increments is at the discretion of the supervising physician. Please note that severe hepatic impairment (Child-Pugh Class C) is listed as contraindication for use of treprostinil, see section 4.3.

Renal impairment
As no clinical studies have been carried out in patients with renal impairment, the treatment recommendations are not established for patients with renal impairment. As treprostinil and its metabolites are excreted mainly through the urinary route, caution is recommended when treating

patients with renal impairment in order to prevent deleterious consequences related to the possible increase of systemic exposure.

Elderly
No pharmacokinetic data of treprostinil in elderly is available. Caution is recommended when treating elderly patients due to higher incidence of hepatic and / or renal impairment.

Obese patients
Therapy of obese patients (weight ≥ 30% above ideal weight) should be initiated and increased with doses calculated based on their ideal weight. See section 5.2 for more information.

Paediatric population
There is no relevant use of treprostinil in children and adolescents for the indication of CTEPH.

Method of administration

Trepulmix is for subcutaneous use. It is administered undiluted by continuous infusion via a subcutaneous catheter using an ambulatory infusion pump.

The healthcare professional responsible for the therapy must ensure that the patient is fully trained and competent to use the chosen infusion device. All patients must be trained in preparation of the treprostinil infusion reservoir and priming of the infusion delivery tubing and connection. Written guidance, either from the pump manufacturer or specially tailored advice by the prescribing physician must be made available to the patient. This includes the required normal drug delivery actions, advice how to manage occlusions and other pump alarms, and details whom to contact in an emergency.

In order to avoid interruptions in drug delivery, the patient must have access to a backup infusion pump and subcutaneous infusion sets in the event that the administration equipment should suffer an accidental malfunction.

The ambulatory infusion pump used to administer undiluted Trepulmix subcutaneously, should be:

- small and lightweight,
- capable of adjusting infusion rates in increments of 0.002 ml/h or less,
- fitted with occlusion, low battery, programming error and motor malfunction alarms,
- accurate to within +/- 6% of the programmed delivery rate
- positive pressure driven (continuous or pulsated).

The reservoir must be made of polypropylene or glass.

Patients must be thoroughly trained in the use and programming of the pump, and the connection and care of the infusion set.

Flushing the infusion line whilst connected to the patient may lead to accidental overdose. For more information on the symptoms and treatment of overdose please refer to Section 4.9 of this document.

Trepulmix is available at concentrations of 1, 2.5, 5 and 10 mg/ml.

For subcutaneous infusion, Trepulmix is delivered without further dilution at a calculated subcutaneous infusion rate (ml/h) based on a patient's dose (ng/kg/min), weight (kg), and the vial strength (mg/ml) of Trepulmix being used. During use a single reservoir (syringe) of undiluted Trepulmix can be administered up to 72 hours at 37 °C. The subcutaneous infusion rate is calculated using the following formula:

$$\textbf{Subcutaneous infusion rate (ml/h)} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006*}}{\textbf{Trepulmix vial strength} \text{ (mg/ml)}}$$

**Conversion factor of 0.00006 = 60 min/hour x 0.000001 mg/ng*

To avoid calculation errors due to the complex formula please check the dose calculation tables below. For each medicinal product strength one dose calculation table is available.

Example calculations for ***subcutaneous infusion*** are as follows:

Example 1:

For a 60 kg person at the recommended initial dose of 1.25 ng/kg/min using the 1 mg/ml Trepulmix vial strength, the infusion rate would be calculated as follows:

$$\textbf{Subcutaneous infusion rate (ml/h)} = \frac{\textbf{1.25 ng}/\text{kg/min} \times \textbf{60 kg} \times \textbf{0.00006}}{\textbf{1} \text{ mg/ml}} = \textbf{0.005} \text{ ml/h}$$

Example 2:

For a 65 kg person at a dose of 40 ng/kg/min using the 5 mg/ml Trepulmix vial strength, the infusion rate would be calculated as follows:

$$\textbf{Subcutaneous infusion rate (ml/h)} = \frac{\textbf{40 ng}/\text{kg/min} \times \textbf{65 kg} \times \textbf{0.00006}}{\textbf{5} \text{ mg/ml}} = \textbf{0.031} \text{ ml/h}$$

Table 1-1 provides guidance for subcutaneous infusion delivery rates of Trepulmix 1 mg/ml for patients of different body weights corresponding to doses of up to 42.5 ng/kg/min.

Table 1-1:

Infusion rate setting of subcutaneous pump (ml/h) for Trepulmix 1 mg/ml

Patient weight (kg)

Dose (ng/kg/min)	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
1.25	0.002	0.002	0.003	0.003	0.003	0.004	0.004	0.005	0.005	0.005	0.006	0.006	0.006	0.007	0.007	0.008
2.5	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
3.75	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021	0.023
5	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
6.25	0.009	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.024	0.026	0.028	0.030	0.032	0.034	0.036	0.038
7.5	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
8.75	0.013	0.016	0.018	0.021	0.024	0.026	0.029	0.032	0.034	0.037	0.039	0.042	0.045	0.047	0.050	0.053
10	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
11.25	0.017	0.020	0.024	0.027	0.030	0.034	0.037	0.041	0.044	0.047	0.051	0.054	0.057	0.061	0.064	0.068
12.5	0.019	0.023	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
13.75	0.021	0.025	0.029	0.033	0.037	0.041	0.045	0.050	0.054	0.058	0.062	0.066	0.070	0.074	0.078	0.083
15	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
16.25	0.024	0.029	0.034	0.039	0.044	0.049	0.054	0.059	0.063	0.068	0.073	0.078	0.083	0.088	0.093	0.098
17.5	0.026	0.032	0.037	0.042	0.047	0.053	0.058	0.063	0.068	0.074	0.079	0.084	0.089	0.095	0.100	0.105
18.75	0.028	0.034	0.039	0.045	0.051	0.056	0.062	0.068	0.073	0.079	0.084	0.090	0.096	0.101	0.107	0.113
20	0.030	0.036	0.042	0.048	0.054	0.060	0.066	0.072	0.078	0.084	0.090	0.096	0.102	0.108	0.114	0.120
21.25	0.032	0.038	0.045	0.051	0.057	0.064	0.070	0.077	0.083	0.089	0.096	0.102	0.108	0.115	0.121	0.128
22.5	0.034	0.041	0.047	0.054	0.061	0.068	0.074	0.081	0.088	0.095	0.101	0.108	0.115	0.122	0.128	0.135
23.75	0.036	0.043	0.050	0.057	0.064	0.071	0.078	0.086	0.093	0.100	0.107	0.114	0.121	0.128	0.135	0.143
25	0.038	0.045	0.053	0.060	0.068	0.075	0.083	0.090	0.098	0.105	0.113	0.120	0.128	0.135	0.143	0.150
27.5	0.041	0.050	0.058	0.066	0.074	0.083	0.091	0.099	0.107	0.116	0.124	0.132	0.140	0.149	0.157	0.165
30	0.045	0.054	0.063	0.072	0.081	0.090	0.099	0.108	0.117	0.126	0.135	0.144	0.153	0.162	0.171	0.180
32.5	0.049	0.059	0.068	0.078	0.088	0.098	0.107	0.117	0.127	0.137	0.146	0.156	0.166	0.176	0.185	0.195
35	0.053	0.063	0.074	0.084	0.095	0.105	0.116	0.126	0.137	0.147	0.158	0.168	0.179	0.189	0.200	0.210
37.5	0.056	0.068	0.079	0.090	0.101	0.113	0.124	0.135	0.147	0.158	0.169	0.180	0.191	0.203	0.214	0.225
40	0.060	0.072	0.084	0.096	0.108	0.120	0.132	0.144	0.156	0.168	0.180	0.192	0.204	0.216	0.228	0.240
42.5	0.064	0.077	0.089	0.102	0.115	0.128	0.140	0.153	0.166	0.179	0.191	0.204	0.217	0.230	0.242	0.255

The shaded areas indicate the highest infusion rate which is possible with a 3 ml syringe change every three days.

Table 1-2 provides guidance for subcutaneous infusion delivery rates of Trepulmix 2.5 mg/ml for patients of different body weights corresponding to doses of up to 42.5 ng/kg/min.

Table 1-2:

Infusion rate setting of subcutaneous pump (ml/h) for Trepulmix 2.5 mg/ml

Patient weight (kg)

Dose (ng/kg/min)	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
5	0.003	0.004	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
6.25	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
7.5	0.005	0.005	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
8.75	0.005	0.006	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
10	0.006	0.007	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
11.25	0.007	0.008	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
12.5	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
13.75	0.008	0.010	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
15	0.009	0.011	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
16.25	0.010	0.012	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
17.5	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
18.75	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
20	0.012	0.014	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
21.25	0.013	0.015	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
22.5	0.014	0.016	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
23.75	0.014	0.017	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
25	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
27.5	0.017	0.020	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
30	0.018	0.022	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
32.5	0.020	0.023	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
35	0.021	0.025	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
37.5	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
40	0.024	0.029	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096
42.5	0.026	0.031	0.036	0.041	0.046	0.051	0.056	0.061	0.066	0.071	0.077	0.082	0.087	0.092	0.097	0.102

The shaded areas indicate the highest infusion rate which is possible with a 3 ml syringe change every three days.

Table 1-3 provides guidance for subcutaneous infusion delivery rates of Trepulmix 5 mg/ml for patients of different body weights corresponding to doses of up to 80 ng/kg/min.

Table 1-3:

Infusion rate setting of subcutaneous pump (ml/h) for Trepulmix 5 mg/ml

Patient weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
10	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
12.5	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
15	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
17.5	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
20	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
22.5	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
25	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
27.5	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
30	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
32.5	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
35	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
37.5	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
40	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
42.5	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
45	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
47.5	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
50	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
55	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
60	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
65	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
70	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
75	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
80	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096

The shaded areas indicate the highest infusion rate which is possible with a 3 ml syringe change every three days.

Table 1-4 provides guidance for subcutaneous infusion delivery rates of Trepulmix 10 mg/ml for patients of different body weights corresponding to doses of up to 155 ng/kg/min.

Table 1-4:

Infusion rate setting of subcutaneous pump (ml/h) for Trepulmix 10 mg/ml

Patient weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
50	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
55	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
60	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
65	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
70	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
75	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
80	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
85	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
90	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
95	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
100	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
105	0.022	0.025	0.028	0.032	0.035	0.038	0.041	0.044	0.047	0.050	0.054	0.057	0.060	0.063
110	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
115	0.024	0.028	0.031	0.035	0.038	0.041	0.045	0.048	0.052	0.055	0.059	0.062	0.066	0.069
120	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
125	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
130	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
135	0.028	0.032	0.036	0.041	0.045	0.049	0.053	0.057	0.061	0.065	0.069	0.073	0.077	0.081
140	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
145	0.030	0.035	0.039	0.044	0.048	0.052	0.057	0.061	0.065	0.070	0.074	0.078	0.083	0.087
150	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
155	0.033	0.037	0.042	0.047	0.051	0.056	0.060	0.065	0.070	0.074	0.079	0.084	0.088	0.093

Shaded areas indicate the highest infusion rate supported by a 3 ml syringe change every three days.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pulmonary veno-occlusive disease.
- Severe decompensated left heart failure.
- Severe hepatic impairment (Child-Pugh Class C).
- Active gastrointestinal ulcer, intracranial haemorrhage, gastrointestinal injury or other gastrointestinal bleeding.
- Congenital or acquired valvular defects with clinically relevant myocardial dysfunction not related to pulmonary hypertension.
- Severe coronary heart disease or unstable angina
- Myocardial infarction within the last six months
- Severe arrhythmias
- Cerebrovascular events (e.g. transient ischaemic attack, stroke) within the last three months.
- Co-administration with other prostanoids

4.4 Special warnings and precautions for use

General therapy

The decision to initiate therapy with treprostinil should take into consideration the high probability that continuous infusion will have to be continued for a prolonged period. Thus the patient's ability to accept and to be responsible for an indwelling catheter and infusion device should be carefully considered. The clinical team responsible for the therapy must ensure that the patient is fully trained and competent to use the chosen infusion device (see section 4.2).

Treprostinil is a potent pulmonary and systemic vasodilator. 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.

If a patient develops pulmonary oedema while on treprostinil, the possibility of a concomitant pulmonary veno-occlusive disease should be considered. The treatment should be stopped as pulmonary veno-occlusive disease is a contraindication for therapy with treprostinil (see section 4.3).

Caution is advised in situations where treprostinil may increase the risk of bleeding by inhibiting platelet aggregation (see section 4.5 and 4.8).

Withdrawal

Abrupt withdrawal or sudden marked reductions in the dose of treprostinil may cause a rebound in pulmonary hypertension (see section 4.2).

Special populations

Patients with hepatic and renal impairment should be dosed cautiously (see section 4.2).

As treprostinil and its metabolites are excreted mainly through the urinary route, caution is recommended when treating patients with renal impairment in order to prevent deleterious consequences related to the possible increase of systemic exposure (see section 4.2).

Concomitant medicinal products

Concomitant administration of cytochrome P450 (CYP2C8) enzyme inhibitors (as gemfibrozil) may lead to increased exposure (both C_{max} and AUC) to treprostinil. With an increased exposure there is a likelihood of a higher incidence of adverse events associated with the administration of treprostinil. Therefore, a dose reduction should be considered (see section 4.5).

Concomitant administration of CYP2C8 enzyme inducers (for example rifampicin) may result in a decreased exposure to treprostinil. At a reduced exposure, it is likely to have decreased clinical efficacy. Therefore, a higher dose of treprostinil is to be considered (see section 4.5).

Sodium content

Trepulmix 1 mg/ml solution for infusion
This medicinal product contains 36.8 mg sodium per 10 ml vial of 1 mg/ml, equivalent to 1.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Trepulmix 2.5 mg/ml solution for infusion
This medicinal product contains 37.3 mg mg sodium per 10 ml vial of 2.5 mg/ml, equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Trepulmix 5 mg/ml solution for infusion
This medicinal product contains 39.1 mg sodium per 10 ml vial of 5 mg/ml, equivalent to 2.0% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Trepulmix 10 mg/ml solution for infusion
This medicinal product contains 37.4 mg sodium per 10 ml vial of 10 mg/ml, equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration with diuretics, antihypertensive agents, or other vasodilators

Concomitant administration of treprostinil with diuretics, antihypertensive agents or other vasodilators increases the risk of systemic hypotension.

Concomitant administration with platelet aggregation inhibitors, including NSAIDs and anticoagulants

Treprostinil may inhibit platelet function. Concomitant administration of treprostinil with platelet aggregation inhibitors**,** including NSAIDs, nitric oxide donors or anticoagulants may increase the risk of bleeding. Surveillance of patients taking anticoagulants should be closely maintained. The concomitant use of other platelet inhibitors should be avoided in patients taking anticoagulants.

Concomitant administration with cytochrome P450 (CYP2C8) enzyme inducers/inhibitors

Gemfibrozil and other CYP2C8 inhibitors
Pharmacokinetic studies in humans with oral treprostinil diolamine indicated that the concomitant administration of cytochrome P450 (CYP2C8) enzyme inhibitor gemfibrozil doubles the exposure (both C_{max} and AUC) to treprostinil. In case a CYP2C8 inhibitor (e.g. gemfibrozil, trimethoprim and deferasirox) is added to or omitted from the patient's treatment after the titration phase, a dose adjustment of treprostinil has to be considered.

Rifampicin and other CYP2C8 inducers
Pharmacokinetic studies in humans with oral treprostinil diolamine indicated that the concomitant administration of CYP2C8 enzyme inducer rifampicin resulted in a reduced (by about 20%) exposure to treprostinil. In case rifampicin is added to or omitted from the patient's treatment after the titration phase, a dose adjustment of treprostinil has to be considered.

Also other CYP2C8 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's Wort) may lead to reduced exposure to treprostinil. In case a CYP2C8 inhibitor is added to or omitted from the patient's treatment after the titration phase, a dose adjustment of treprostinil has to be considered.

Concomitant administration with bosentan

In a pharmacokinetic study in humans, in which bosentan (250 mg/day) and treprostinil diolamine (oral dose of 2 mg/day) were administered concomitantly, no pharmacokinetic interaction between treprostinil and bosentan was observed.

Concomitant administration with sildenafil

In a pharmacokinetic study in humans, in which sildenafil (60mg/day) and treprostinil diolamine (oral dose of 2 mg/day) were administered concomitantly, no pharmacokinetic interaction between treprostinil and sildenafil was observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of treprostinil in pregnant women. Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). Treprostinil should only be used during pregnancy if the potential benefit to the mother justifies the potential risk to the foetus.

Women of child-bearing potential

Contraception is recommended during treprostinil treatment.

Breast-feeding

It is not known whether treprostinil is excreted in human milk. Breastfeeding women taking treprostinil should be advised to discontinue breastfeeding.

4.7 Effects on ability to drive and use machines

Trepulmix has minor influence on the ability to drive and use machines at the initiation of treatment or dose adjustments. They may be accompanied by undesirable effects such as symptomatic systemic hypotension or dizziness which may impair ability to drive and operate machinery.

4.8 Undesirable effects

Summary of safety profile

In addition to local effects resulting from the administration of treprostinil by subcutaneous infusion such as infusion site pain and infusion site reaction, adverse reactions with treprostinil are related to the pharmacological properties of prostacyclins.

Tabulated summary of adverse reactions

The adverse reactions are presented as MedDRA preferred terms under the MedDRA system organ class. The incidence of the adverse reactions below are expressed according to the following categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000).

System organ class	**Adverse reaction**	**Incidence**
Nervous system disorders	Headache	Very common
	Dizziness	Common
Eye disorders	Eyelid oedema	Uncommon
Cardiac disorders	Vasodilatation	Very common
	Hypotension	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Dyspepsia	Uncommon
	Vomiting	Uncommon
Skin and subcutaneous tissue disorders	Rash	Common
	Pruritus	Uncommon
	Exanthema	Uncommon
Musculoskeletal, connective tissue disorders	Jaw pain	Very common
	Myalgia, arthralgia	Common
	Pain in extremities	Common
	Back pain	Uncommon
General disorders and administration site conditions	Infusion site pain, infusion site reaction, bleeding or haematoma	Very common
	Infusion site abscess	Common

	Infusion site infection	Common
	Oedema	Common
	Flushing	Common
	Decreased appetite	Uncommon
	Fatigue	Uncommon

Description of selected adverse reactions
Bleeding events
Due to its effects on platelet aggregation, treprostinil may increase the risk of bleeding, as observed by an increased incidence of epistaxis and gastrointestinal (GI) bleeding (including GI haemorrhage, rectal haemorrhage, gum haemorrhage and melaena) in controlled clinical trials in PAH.

Events observed during clinical practice:

In addition to adverse reactions reported from clinical trials in PAH patients, the following events have been identified during post-approval use of treprostinil in other indications. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The following events were reported:, thrombocytopenia, bone pain.

In addition, generalised rashes, sometimes macular or papular in nature, and cellulitis have been infrequently reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V..

4.9 Overdose

Symptoms of overdose with treprostinil include flushing, headache, hypotension, nausea, vomiting, and diarrhoea. Patients 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 medical control and patients monitored closely for recurrence of unwanted symptoms.

No antidote is known.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excl. heparin
ATC code: B01AC21

Mechanism of action

Treprostinil is a prostacyclin analogue.
It exerts a direct vasodilation effect on the pulmonary and systemic arterial circulation and, inhibits platelet aggregation.

Clinical efficacy and safety

In a randomised, multi-centre, 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 pulmonary

endarterectomy (18-88 years of age, mean 64 years) were treated. Patients were required to have CTEPH classified as severe, as defined by an un-encouraged six-minute walk test (6MWT) of between 150 and 400 meters and a classification in the WHO/NYHA functional class III or IV. Patients were divided into two treprostinil treatment groups (53 high dose and 52 low dose patients, treated with subcutaneous infusion for a total of 24 weeks) as follows. In the high dose group, patients were administered a subcutaneous 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 primary efficacy analysis was based on the individual difference between the 6MWT data at baseline and after 24 weeks. Treprostinil improved the six-minute walk distance (6MWT, six-minute walk test: baseline vs. 24 weeks of treatment) by a mean of 45.43 m in the high dose group versus 3.83 m in the low dose group ($p < 0.05$, ANCOVA). Exploratory secondary efficacy (low vs. high) measures, after 24 weeks of treatment, showed -significant improvements in New York Heart Association functional (NYHA) class, haemodynamic parameters (mean pulmonary vascular resistance, mean pulmonary arterial pressure, mean cardiac output, and mean cardiac index) and median pro-BNP (brain natriuretic peptide values) in favor of the high dose group. No significant differences between the two test groups in the number of patients showing a "clinical worsening", defined as a reduction of 6MWD of 20% compared to baseline, worsening of NYHA functional class and/or hospitalisation due to CTEPH with the need of additional pulmonary hypertension specific treatment, were observed. High dose treprostinil showed no significant changes in the Borg Dyspnoea Score (measured during the 6MWT), or the summed Quality of Life score as assessed by the Minnesota Living with Heart Failure Questionnaire.

5.2 Pharmacokinetic properties

Distribution

In humans, steady-state plasma concentrations are usually achieved within 15 to 18 hours of the initiation of either subcutaneous or intravenous infusion of treprostinil. Steady-state plasma concentrations of treprostinil are dose-proportional at infusion rates of 2.5 up to 125 ng/kg/min.

The mean apparent elimination half-life following subcutaneous administration ranged from 1.32 to 1.42 hours after infusions over 6 hours, 4.61 hours after infusions over 72 hours, and 2.93 hours after infusions lasting at least three weeks. The mean volume of distribution for treprostinil ranged from 1.11 to 1.22 l/kg, and plasma clearance ranged from 586.2 to 646.9 ml/kg/h. Clearance is lower in obese subjects (body mass index (BMI) > 30 kg/m^2).

In a seven-day chronic pharmacokinetic study in 14 healthy volunteers with treprostinil doses ranging from 2.5 to 15 ng/kg/min administered by subcutaneous infusion, steady state plasma treprostinil concentrations reached peak levels twice (at 1 a.m. and 10 a.m. respectively) and trough levels twice (at 7 a.m. and 4 p.m. respectively). The peak concentrations were approximately 20% to 30% higher than the trough concentrations.

Elimination

In a study conducted on healthy volunteers using [^{14}C] radioactive treprostinil, 78.6% and 13.4% of the subcutaneous radioactive dose were recovered in the urine and faeces respectively over a period of 224 hours. No single major metabolite was observed. Five metabolites were detected in the urine, ranging from 10.2% to 15.5% of the dose administered. These five metabolites accounted for a combined total of 64.4%. Three are products of oxidation of the 3-hydroxyloctyl side chain, one is a glucuroconjugated derivative (treprostinil glucuronide) and one is unidentified. Only 3.7% of the dose was recovered in the urine as unchanged parent drug.

An *in vitro* study demonstrated no inhibitory potential of treprostinil to human hepatic microsomal cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A).

Moreover, administration of treprostinil had no inducing effect on hepatic microsomal protein, total cytochrome (CYP) P 450 content or on the activities of the isoenzymes CYP1A, CYP2B and CYP3A.

Hepatic insufficiency

In patients with portopulmonary hypertension and mild (n=4) or moderate (n=5) hepatic insufficiency, treprostinil at a subcutaneous dose of 10 ng/kg/min for 150 minutes had an $AUC_{0\text{-}24\ h}$ that was increased 260 % and 510 %, respectively, compared to healthy subjects. Clearance in patients with hepatic insufficiency was reduced by up to 80% compared to healthy adults (see section 4.2).

Elderly patients

In a multivariate analysis of pooled studies, patients in the age group ≥ 65 years had a small reduction in plasma clearance of treprostinil. However, most publications regarded either healthy volunteers or patient with PAH. CTEPH patients were rarely described. Age stratification was not performed in any publication. As only few studies reported on PK parameters but none reported both on CTEPH indication and PK data, no information is available on the pharmacokinetics of treprostinil in elderly patients.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction.

In 13 and 26 week studies continuous subcutaneous infusions of treprostinil sodium caused infusion site reactions in rats and dogs (oedema/erythema, masses/swellings, pain/sensitivity to touch). In dogs severe clinical effects (hypoactivity, emesis, loose stool and infusion site oedema) and death (associated with intestinal intussusceptions and rectal prolapse) were observed in animals administered ≥ 300ng/kg/min. Mean steady state plasma treprostinil levels of 7.85 ng/ml were measured in these animals. Plasma levels of this order may be achieved in humans treated with treprostinil infusions at > 50ng/kg/min.

As a continuously sufficient exposure to treprostinil has not been proven for any dose tested in the reproductive studies in rats, these studies might be insufficient regarding possible effects on fertility, prenatal and postnatal development.

No long-term animal studies have been performed to evaluate treprostinil's carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Hydrochloric acid
Metacresol
Sodium hydroxide
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

3 years.

After first opening

30 days.

During use with continuous subcutaneous infusion

Chemical, physical and microbial in-use stability of a single container (syringe) of undiluted Trepulmix administered subcutaneously has been demonstrated for 72 h at 37 °C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Trepulmix 1 mg/ml solution for infusion

10 ml type I clear glass vial sealed with a rubber teflon- coated stopper and fitted with a yellow cap.

Trepulmix 2.5 mg/ml solution for infusion

10 ml type I clear glass vial sealed with a rubber teflon- coated stopper and fitted with a blue cap.

Trepulmix 5 mg/ml solution for infusion

10 ml type I clear glass vial sealed with a rubber teflon- coated stopper and fitted with a green cap.

Trepulmix 10 mg/ml solution for infusion

10 ml type I clear glass vial sealed with a rubber teflon- coated stopper and fitted with a red cap.

Each carton contains one vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SciPharm Sàrl
7, Fausermillen
L-6689 Mertert
Luxembourg

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1419/001
EU/1/19/1419/002
EU/1/19/1419/003
EU/1/19/1419/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 April 2020
Date of latest renewal: 13 December 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
1190 Vienna
Austria

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX – 1 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

Trepulmix 1 mg/ml solution for infusion
treprostinil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution for infusion contains 1 mg treprostinil (as treprostinil sodium).

Each 10 ml vial contains 10 mg treprostinil (as treprostinil sodium).

3. LIST OF EXCIPIENTS

Sodium citrate, sodium chloride, sodium hydroxide, hydrochloric acid, metacresol and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

Contains 1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SciPharm Sàrl
7, Fausermillen
L-6689 Mertert
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1419/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – 1 mg/ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trepulmix 1 mg/ml solution for infusion
treprostinil
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg/10 ml

6. OTHER

SciPharm (Logo)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX – 2.5 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

Trepulmix 2.5 mg/ml solution for infusion
treprostinil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution for infusion contains 2.5 mg treprostinil (as treprostinil sodium).

Each 10 ml vial contains 25 mg of treprostinil (as treprostinil sodium).

3. LIST OF EXCIPIENTS

Sodium citrate, sodium chloride, sodium hydroxide, hydrochloric acid, metacresol and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

Contains 1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SciPharm Sàrl
7, Fausermillen
L-6689 Mertert
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1419/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – 2.5 mg/ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trepulmix 2.5 mg/ml solution for infusion
treprostinil
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 mg/10 ml

6. OTHER

SciPharm (Logo)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX – 5 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

Trepulmix 5 mg/ml solution for infusion
treprostinil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution for infusion contains 5 mg treprostinil (as treprostinil sodium).

Each 10 ml vial contains 50 mg of treprostinil (as treprostinil sodium).

3. LIST OF EXCIPIENTS

Sodium citrate, sodium chloride, sodium hydroxide, hydrochloric acid, metacresol and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

Contains 1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SciPharm Sàrl
7, Fausermillen
L-6689 Mertert
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1419/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – 5 mg/ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trepulmix 5 mg/ml solution for infusion
treprostinil
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg/10 ml

6. OTHER

SciPharm (Logo)

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX – 10 mg/ml

1. NAME OF THE MEDICINAL PRODUCT

Trepulmix 10 mg/ml solution for infusion
treprostinil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of solution for infusion contains 10 mg treprostinil (as treprostinil sodium).

Each 10 ml vial contains 100 mg of treprostinil (as treprostinil sodium).

3. LIST OF EXCIPIENTS

Sodium citrate, sodium chloride, sodium hydroxide, hydrochloric acid, metacresol and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion.

Contains 1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SciPharm Sàrl
7, Fausermillen
L-6689 Mertert
Luxembourg

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1419/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL – 10 mg/ml

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trepulmix 10 mg/ml solution for infusion
treprostinil
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/10 ml

6. OTHER

SciPharm (Logo)

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

treprostinil

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trepulmix is and what it is used for

What Trepulmix is
The active substance of Trepulmix is treprostinil.
Treprostinil belongs to a group of medicines which work in a similar way to the naturally occurring prostacyclins. Prostacyclins are hormone-like substances which reduce blood pressure by relaxing blood vessels, causing them to widen, which allows the blood to flow more easily. Prostacyclins can also have an influence in preventing blood from clotting.

What Trepulmix is used to treat
Trepulmix is used for the 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. Chronic thromboembolic pulmonary 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.

How Trepulmix works
Trepulmix lowers blood pressure within the pulmonary artery by improving blood flow and reducing the amount of work for the heart. Improved blood flow leads to an increased supply of oxygen to the body and reduced strain on the heart, causing it to function more effectively. Trepulmix improves the symptoms associated with CTEPH and the ability to exercise in patients who are limited in terms of activity.

2. What you need to know before you use Trepulmix

Do not use Trepulmix

- if you are allergic to treprostinil or any of the other ingredients of this medicine (listed in section 6).
- if you have been diagnosed with a disease called “pulmonary veno-occlusive disease”. This is a disease in which the blood vessels that carry blood through your lungs become swollen and clogged resulting in a higher pressure in the blood vessels between the heart and the lungs.
- if you have severe liver disease
- if you have a heart problem, for example:
    - a heart attack (myocardial infarction) within the last six months
    - severe changes in heart rate
    - severe coronary heart disease or unstable angina
    - a heart defect has been diagnosed, such as a faulty heart valve that causes the heart to work poorly
    - any disease of the heart which is not being treated or not under close medical observation
- if you are at a specific high risk of bleeding – for example active stomach ulcers, injuries or other bleeding conditions
- if you have had a stroke within the last 3 months, or any other interruption of blood supply to the brain

Warnings and precautions
Talk to your doctor before using Trepulmix if you:
- suffer from any liver disease
- suffer from kidney disease
- have been advised that you are medically obese (BMI greater than 30 kg/m^2)
- are on a low sodium diet

During your treatment with Trepulmix, tell your doctor:
- if your blood pressure decreases (hypotension)
- if you experience a rapid increase in breathing difficulties or persistent cough (this can be related to congestion in the lungs or asthma or other condition), **consult your doctor immediately.**
- if you have excessive bleeding as treprostinil may increase the risk, by preventing your blood from clotting

Children and adolescents
Trepulmix must not be used in children and adolescents.

Other medicines and Trepulmix
Tell your doctor if you are taking/using, have recently taken/used or might take/use any other medicines. Please tell your doctor if you are taking:
- medicines used to treat **high blood pressure** (antihypertensive medicines or other vasodilators)
- medicines used to increase the rate of **urination** (diuretics) including furosemide
- medicines that stop **blood clotting** (anticoagulants) such as warfarin, heparin or nitric oxide based products
- any non-steroidal anti-inflammatory (**NSAID**) medicines (e.g. acetylsalicylic acid, ibuprofen)
- medicines which may enhance or weaken the effects of Trepulmix (e.g. gemfibrozil, rifampicin, trimethoprim, deferasirox, phenytoin, carbamazepine, phenobarbital, St. John's wort.), as your doctor may need to adjust the dosage of Trepulmix.

Pregnancy and breast-feeding
Trepulmix is not recommended if you are pregnant, planning to become pregnant, or think that you might be pregnant, unless considered essential by your doctor. The safety of this medicine for use during pregnancy has not been established.

Contraception is strongly recommended during Trepulmix treatment.

Trepulmix is not recommended for use in breast-feeding, unless considered essential by your doctor. You are advised to stop breast-feeding if Trepulmix is prescribed for you, because it is not known whether this medicine passes into breast milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Driving and using machines
Trepulmix may induce low blood pressure with dizziness or fainting. In such a case do not drive or operate machinery and ask your doctor for advice.

Trepulmix contains sodium
Please tell your doctor if you are on a controlled sodium diet. They will take into account:

Trepulmix 1 mg/ml solution for infusion
This medicine contains 36.8 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.8% of the recommended maximum daily dietary intake of sodium for an adult.

Trepulmix 2.5 mg/ml solution for infusion
This medicine contains 37.3 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.9% of the recommended maximum daily dietary intake of sodium for an adult.

Trepulmix 5 mg/ml solution for infusion
This medicine contains 39.1 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.0% of the recommended maximum daily dietary intake of sodium for an adult.

Trepulmix 10 mg/ml solution for infusion
This medicine contains 37.4 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.9% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Trepulmix

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Trepulmix is administered undiluted as a continuous subcutaneous infusion (under the skin) via a small tube (cannula) which is located in your abdomen or thigh;

Trepulmix is pushed through the tubing by a portable pump.

Before you leave the hospital or clinic, your doctor will tell you how to prepare Trepulmix and at what rate the pump should deliver your treprostinil. Information on how to use the pump correctly and what to do if it stops working should also be given to you. The information should also tell you who to contact in an emergency.
Flushing of the infusion line whilst connected may cause accidental overdose.

Adult patients
Trepulmix is available as 1 mg/ml, 2.5 mg/ml, 5 mg/ml or 10 mg/ml solution for infusion. Your doctor will determine the infusion rate and dose appropriate for your condition.

Elderly patients
No special dose adjustments are necessary for these patients.

Patients with liver or kidney disease
Your doctor will determine the infusion rate and dose appropriate for your condition.

Infusion rate
The infusion rate can be reduced or increased on an individual basis under **medical supervision only**.

The aim of adjusting the infusion rate is to establish an effective maintenance rate which improves symptoms of CTEPH while minimising any undesirable effects.

If your symptoms increase or if you need complete rest, or are confined to your bed or chair, or if any physical activity brings on discomfort and your symptoms occur at rest, do not increase your dose without medical advice. Trepulmix may no longer be sufficient to treat your disease and another treatment may be required.

If you use more Trepulmix than you should
If you accidentally overdose Trepulmix, you may experience nausea, vomiting, diarrhoea, low blood pressure (dizziness, light-headedness or fainting), skin flushes and/or headaches.

If any of these effects become severe you should contact your doctor or hospital immediately. Your doctor may reduce or discontinue the infusion until your symptoms have disappeared. Trepulmix solution for infusion will then be reintroduced at a dose level recommended by your doctor.

If you stop using Trepulmix
Always use Trepulmix as directed by your doctor or hospital specialist. Do not stop using Trepulmix unless your doctor has advised you to.

Abrupt withdrawal or sudden reductions in the dose of Trepulmix may cause the pulmonary arterial hypertension to return with the potential for rapid and severe deterioration in your condition.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common (may affect more than 1 in 10people)
- widening of blood vessels
- pain around the infusion site
- reaction around the infusion site
- bleeding or bruising around the infusion site
- headaches
- nausea
- diarrhoea
- jaw pain

Common (may affect up to 1 in 10 people)
- dizziness
- light-headedness or fainting due to low blood pressure
- skin rashes
- infusion site infection
- pus around infusion site (abscess)
- muscle pain (myalgia)
- joint pain (arthralgia)
- swelling of feet, ankles, legs or fluid retention
- hot flush

- pain in arms and / or legs

Uncommon (may affect up to 1 in 100 people)
- swollen eyelids (eyelid oedema)
- indigestions
- vomiting
- skin itches
- exanthema
- back pain
- decreased appetite
- tiredness

Other possible side effects observed in pulmonary arterial hypertension (PAH) patients:
- bleeding episodes such as: as nose bleeds, coughing up blood, blood in the urine, bleeding from the gums, blood in the faeces

Other possible side effects observed during clinical practice:
- a decrease of blood clotting cells (platelets) in the blood (thrombocytopenia)
- bone pain
- skin rashes with discolouration or raised bumps
- tissue infection under the skin (cellulitis)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Trepulmix

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date that is stated on the carton and vial after "EXP". The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

A Trepulmix vial must be used or discarded within 30 days after first opening.

During continuous subcutaneous infusion, a single reservoir (syringe) of undiluted Trepulmix must be used within 72 hours.

Do not use this medicine if you notice any damage to the vial, discolouration or other signs of deterioration.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Trepulmix contains
The active substance is treprostinil.

Trepulmix 1 mg/ml solution for infusion
Each ml of solution contains 1 mg treprostinil (as sodium salt).
Each 10 ml vial of solution contains 10 mg treprostinil (as sodium salt).

Trepulmix 2.5 mg/ml solution for infusion
Each ml of solution contains 2.5 mg treprostinil (as sodium salt)
Each 10 ml vial of solution contains 25 mg treprostinil (as sodium salt).

Trepulmix 5 mg/ml solution for infusion
Each ml of solution contains 5 mg treprostinil (as sodium salt).
Each 10 ml vial of solution contains 50 mg treprostinil (as sodium salt).

Trepulmix 10 mg/ml solution for infusion
Each ml of solution contains 10 mg treprostinil (as sodium salt).
Each 10 ml vial of solution contains 100 mg treprostinil (as sodium salt).

The other ingredients are:
Sodium citrate, sodium chloride, sodium hydroxide, hydrochloric acid, metacresol and water for injections. See section 2, "Trepulmix contains sodium".

What Trepulmix looks like and the contents of the pack
Trepulmix is a clear colourless to slightly yellow solution, available in a 10 ml clear glass vial sealed with a rubber stopper and a colour coded cap:

Trepulmix 1 mg/ml solution for infusion
Trepulmix 1 mg/ml solution for infusion has a yellow rubber cap.

Trepulmix 2.5 mg/ml solution for infusion
Trepulmix 2.5 mg/ml solution for infusion has a blue rubber cap.

Trepulmix 5 mg/ml solution for infusion
Trepulmix 5 mg/ml solution for infusion has a green rubber cap.

Trepulmix 10 mg/ml solution for infusion
Trepulmix 10 mg/ml solution for infusion has a red rubber cap.

Each carton contains one vial.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
SciPharm Sàrl
7, Fausermillen
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Luxembourg

Manufacturer
AOP Orphan Pharmaceuticals GmbH
Leopold-Ungar-Platz 2
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Austria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.