SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Treposuvi 2.5 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2.5 mg treprostinil, as treprostinil sodium.

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

Excipients with known effect: sodium: 37.3 mg (1.62 mmol) per 10 ml vial

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion:

Clear colourless to slightly yellow, isotonic solution, free from visible particles, with pH value between 6.0 and 7.2.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of idiopathic or heritable pulmonary arterial hypertension (PAH) to improve exercise tolerance and symptoms of the disease in patients classified as New York Heart Association (NYHA) functional class III.

4.2 Posology and method of administration

Posology

Treposuvi is administered by continuous subcutaneous or intravenous infusion. Due to the risks associated with chronic indwelling central venous catheters, including serious blood stream infections, subcutaneous infusion (undiluted) is the preferred mode of administration and continuous intravenous infusion should be reserved for

patients stabilised with treprostinil subcutaneous infusion and who become intolerant of the subcutaneous route, and in whom these risks are considered acceptable.

The treatment should be initiated and monitored only by clinicians experienced in the treatment of pulmonary hypertension.

Adults

Treatment initiation for patients new to prostacyclin therapy
Treatment should be initiated under close medical supervision in a medical setting able to provide intensive care.

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 1.25 ng/kg/min per week for the first four weeks of treatment and then 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.

Efficacy in the main 12-week trials was only maintained if the dose was increased on average 3-4 times per month. The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, whilst minimising the excessive pharmacological effects of treprostinil.

Adverse effects, such as flushing, headache, hypotension, nausea, vomiting and diarrhoea, are generally dependent on the dose of treprostinil administered. They may disappear as treatment continues, but should they persist or become intolerable to the patient, the infusion rate may be reduced to diminish their intensity.

During follow-up phases of clinical trials, 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.

For patients with obesity (weighing $\geq$ 30% more than ideal body weight) initial dose and following dose increments should be based on ideal body weight.

Abrupt withdrawal or sudden marked reductions in the dose of treprostinil may cause a rebound in pulmonary arterial 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 a few hours, restarting of treprostinil infusion can be done using the same dose rate; interruptions for longer periods may require the dose of treprostinil to be re-titrated.

Elderly

Clinical studies of treprostinil did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. In a population pharmacokinetic (PK) analysis, plasma clearance of treprostinil was reduced by 20%. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Paediatric population

There are few data in patients less than 18 years of age. Available clinical studies do not establish whether the efficacy and safety of the recommended posology scheme for adults can be extrapolated to children and adolescents.

At risk populations

Hepatic impairment
Plasma treprostinil exposure (area under the plasma concentration-time curve; AUC) increases by 260% to 510% in mild to moderate hepatic impairment, Child-Pugh classes A and B, respectively. Plasma clearance of treprostinil was reduced up to 80% in subjects presenting with mild to moderate hepatic impairment. Caution is therefore advised when treating patients with hepatic impairment because of the risk of an increase in systemic exposure which may reduce tolerability and lead to an increase in dose-dependent adverse effects.

The initial dose of treprostinil should be decreased to 0.625 ng/kg/min and incremental dose increases should be made cautiously.

Renal impairment
No dose adjustments are required in patients with renal impairment. Treprostinil is not cleared by dialysis *[see Pharmacokinetic properties (5.2)]*.

Method of transition to intravenous epoprostenol treatment

When transition to intravenous epoprostenol is required, the transition phase should be carried out under strict medical supervision. It may be useful for guidance purposes to note the following suggested treatment transition scheme. Treprostinil infusions should first be decreased slowly by 2.5 ng/kg/min. After at least 1 hour at the new treprostinil dose, epoprostenol treatment can be initiated at a maximum dose of 2 ng/kg/min. The treprostinil dose should then be decreased at subsequent intervals of at least 2 hours, and at the same time the epoprostenol dose is gradually increased after maintaining the initial dose for at least one hour.

Method of administration

Administration by continuous subcutaneous infusion

Treposuvi is administered by continuous subcutaneous infusion via a subcutaneous catheter using an ambulatory infusion pump.

In order to avoid potential 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 Treposuvi subcutaneously, should be:

1) small and lightweight,

2) capable of adjusting infusion rates in increments of approximately 0.002 ml/h,

3) fitted with occlusion, low battery, programming error and motor malfunction alarms,

4) accurate to within +/- 6% of the programmed delivery rate

5) 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.

Infusion rates ∇ (ml/h) are calculated using the following formula:

∇ (ml/h) = D (ng/kg/min) x W (kg) x [0.00006/treprostinil concentration (mg/ml)]

D = prescribed dose expressed in ng/kg/min
W = body weight of the patient expressed in kg

Treposuvi exists at concentrations of 1, 2.5, 5 and 10 mg/ml.

For subcutaneous infusion, Treposuvi 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 Treposuvi being used. During use, a single reservoir (syringe) of undiluted Treposuvi can be administered up to 14 days at 37°C. The Subcutaneous Infusion rate is calculated using the following formula:

$$\textbf{Subcutaneous Infusion Rate (ml/h)} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006*}}{\textbf{Treposuvi Vial Strength} \text{ (mg/ml)}}$$

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

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 Treposuvi Vial Strength, the infusion rate would be calculated as follows:

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

Example 2:

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

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

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

Table 1:

Infusion rate setting of subcutaneous pump (ml/h) for Treposuvi at a treprostinil concentration of 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

Administration by continuous intravenous infusion with an external ambulatory pump

Treposuvi is administered by continuous intravenous infusion, via a central venous catheter, using an external ambulatory infusion pump. It may also be administered temporarily via a peripheral venous cannula, preferably placed in a large vein. Use of a peripheral infusion for more than a few hours may be associated with an increased risk of thrombophlebitis (see section 4.8).

In order to avoid potential interruptions in drug delivery, the patient must have access to a backup infusion pump and infusion sets in the event that the administration equipment malfunctions.

In general, the external ambulatory infusion pump used to administer diluted Treposuvi intravenously should:

1) be small and lightweight,

2) be capable of adjusting infusion rates in increments of approximately 0.05 ml/h. Typical flow rates would be between 0.4 ml and 2 ml per hour;

3) have occlusion / no delivery, low battery, programming error and motor malfunction alarms,

4) have delivery accuracy of ±6% or better of the hourly dose

5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Treposuvi should be diluted with either sterile Water for Injection or 0.9% (w/v) Sodium Chloride for Injection and is administered intravenously by continuous infusion, via a surgically placed indwelling central venous catheter or temporarily via a peripheral venous cannula, using an infusion pump designed for intravenous drug delivery.

When using an appropriate external ambulatory infusion pump and reservoir, a predetermined intravenous infusion rate should first be selected to allow for a desired

infusion period. The maximum duration of use of diluted Treposuvi should be no more than 24 hours (see section 6.3)

Typical intravenous infusion system reservoirs have volumes of 20, 50 or 100 ml. After determination of the required Intravenous Infusion Rate (ml/h) and the patient's Dose (ng/kg/min) and Weight (kg), the Diluted Intravenous treprostinil Concentration (mg/ml) can be calculated using the following formula:

Step 1

$$\textbf{Diluted Intravenous treprostinil Concentration} \text{ (mg/ml)} = \frac{\textbf{Dose} \text{ (ng/kg/min)} \times \textbf{Weight} \text{ (kg)} \times \textbf{0.00006}}{\textbf{Intravenous Infusion Rate} \text{ (ml/h)}}$$

The amount of Treposuvi needed to make the required Diluted Intravenous treprostinil Concentration for the given reservoir size can then be calculated using the following formula:

Step 2

$$\textbf{Amount of Treposuvi} \text{ (ml)} = \frac{\textbf{Diluted Intravenous treprostinil Concentration} \text{ (mg/ml)}}{\textbf{Treposuvi Vial Strength} \text{ (mg/ml)}} \times \textbf{Total Volume of Diluted treprostinil Solution in Reservoir} \text{ (ml)}$$

The calculated amount of Treposuvi is then added to the reservoir along with a sufficient volume of diluent (Sterile Water for Injection or 0.9% Sodium Chloride for Injection) to achieve the desired total volume in the reservoir.

Example calculations for ***Intravenous Infusion*** are as follows:

Example 3:
For a 60 kg person at a dose of 5 ng/kg/min, with a predetermined intravenous infusion rate of 1 ml/h and a reservoir of 50 ml, the Diluted Intravenous treprostinil Solution Concentration would be calculated as follows:

Step 1

$$\textbf{Diluted Intravenous treprostinil Concentration (mg/ml)} = \frac{\textbf{5}\ \text{ng/kg/min} \times \textbf{60}\ \text{kg} \times \textbf{0.0000 6}}{\textbf{1}\ \text{ml/h}} = \textbf{0.018}\ \text{mg/ml}\ (18{,}000\ \text{ng/ml})$$

The amount of Treposuvi (using 1 mg/ml Vial Strength) needed for a total Diluted treprostinil Concentration of 0.018 mg/ml and a total volume of 50 ml would be calculated as follows:

Step 2

$$\textbf{Amount of Treposuvi (ml)} = \frac{\textbf{0.018}\ \text{mg/ml}}{\textbf{1}\ \text{mg/ml}} \times \textbf{50}\ \text{ml} = \textbf{0.9}\ \text{ml}$$

The Diluted Intravenous treprostinil Concentration for the person in Example 3 would thus be prepared by adding 0.9 ml of 1 mg/ml Treposuvi to a suitable reservoir along with a sufficient volume of diluent to achieve a total volume of 50 ml in the reservoir. The pump flow rate for this example would be set at 1 ml/h.

Example 4:

For a 75 kg person at a dose of 30 ng/kg/min, with a predetermined intravenous infusion rate of 2 ml/h, and a reservoir of 100 ml, the Diluted Intravenous treprostinil Solution Concentration would be calculated as follows:

Step 1

$$\textbf{Diluted Intravenous treprostinil Concentration (mg/ml)} = \frac{\textbf{30}\ \text{ng/kg/min} \times \textbf{75}\ \text{kg} \times \textbf{0.0000 6}}{\textbf{2}\ \text{ml/h}} = \textbf{0.0675}\ \text{mg/ml}\ (67{,}500\ \text{ng/ml})$$

The amount of Treposuvi (using 2.5 mg/ml vial strength) needed for a total Diluted treprostinil Concentration of 0.0675 mg/ml and a total volume of 100 ml would be calculated as follows:

Step 2

$$\textbf{Amount of Treposuvi (ml)} = \frac{\textbf{0.0675}\ \text{mg/ml}}{\textbf{2.5}\ \text{mg/ml}} \times \textbf{100}\ \text{ml} = \textbf{2.7}\ \text{ml}$$

The Diluted Intravenous treprostinil Concentration for the person in Example 4 would thus be prepared by adding 2.7 ml of 2.5 mg/ml Treposuvi to a suitable reservoir

along with a sufficient volume of diluent to achieve a total volume of 100 ml in the reservoir. The pump flow rate for this example would be set at 2 ml/h.

Table 2 provides guidance for the volume (ml) of Treposuvi 2.5 mg/ml to be diluted in 20 ml, 50 ml or 100 ml reservoirs (0.4, 1 or 2 ml/h infusion rates, respectively) for patients of differing body weights corresponding to doses of up to 42.5 ng/kg/min.

Table 2:

Volume (ml) of Treposuvi 2.5 mg/ml to be diluted in cassettes or syringes 20 ml (0.4 ml/h infusion rate), 50 ml (1 ml/h infusion rate), 100 ml cassette (2 ml/h infusion rate)

Dose (ng/kg/min)	Patient Weight(kg)															
	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
5	0.150	0.180	0.210	0.240	0.270	0.300	0.330	0.360	0.390	0.420	0.450	0.480	0.510	0.540	0.570	0.60
6.25	0.188	0.225	0.263	0.300	0.338	0.375	0.413	0.450	0.488	0.525	0.563	0.600	0.638	0.675	0.7125	0.75
7.5	0.225	0.270	0.315	0.360	0.405	0.450	0.495	0.540	0.585	0.630	0.675	0.720	0.765	0.810	0.855	0.900
8.75	0.263	0.315	0.368	0.420	0.473	0.525	0.578	0.630	0.683	0.735	0.788	0.840	0.893	0.945	0.998	1.050
10	0.300	0.360	0.420	0.480	0.540	0.600	0.660	0.720	0.780	0.840	0.900	0.960	1.020	1.080	1.140	1.200
11.25	0.334	0.405	0.473	0.540	0.608	0.675	0.743	0.810	0.878	0.945	1.013	1.080	1.148	1.215	1.283	1.350
12.5	0.375	0.450	0.525	0.600	0.675	0.750	0.825	0.900	0.975	1.050	1.125	1.200	1.275	1.350	1.425	1.500
13.75	0.413	0.495	0.578	0.660	0.743	0.825	0.908	0.990	1.073	1.155	1.238	1.320	1.403	1.485	1.568	1.650
15	0.450	0.540	0.630	0.720	0.810	0.900	0.990	1.080	1.170	1.260	1.350	1.440	1.530	1.620	1.710	1.800
16.25	0.488	0.585	0.683	0.780	0.878	0.975	1.073	1.170	1.268	1.365	1.463	1.560	1.658	1.755	1.853	1.950
17.5	0.525	0.630	0.735	0.840	0.945	1.050	1.155	1.260	1.365	1.470	1.575	1.680	1.785	1.890	1.995	2.100
18.75	0.563	0.675	0.788	0.900	1.013	1.125	1.238	1.350	1.463	1.575	1.688	1.800	1.913	2.025	2.138	2.250
20	0.600	0.720	0.840	0.960	1.080	1.200	1.320	1.440	1.560	1.680	1.800	1.920	2.040	2.160	2.280	2.400
21.25	0.638	0.765	0.893	1.020	1.148	1.275	1.403	1.530	1.658	1.785	1.913	2.040	2.168	2.295	2.423	2.550
22.5	0.675	0.810	0.945	1.080	1.215	1.350	1.485	1.620	1.755	1.890	2.025	2.160	2.295	2.430	2.565	2.700
23.75	0.713	0.855	0.998	1.140	1.283	1.425	1.568	1.710	1.853	1.995	2.138	2.280	2.423	2.565	2.708	2.850
25	0.750	0.900	1.050	1.200	1.350	1.500	1.650	1.800	1.950	2.100	2.250	2.400	2.550	2.700	2.850	3.000
27.5	0.825	0.990	1.155	1.320	1.485	1.650	1.815	1.980	2.145	2.310	2.475	2.640	2.805	2.970	3.135	3.300
30	0.900	1.080	1.260	1.440	1.620	1.800	1.980	2.160	2.340	2.520	2.700	2.880	3.060	3.240	3.420	3.600
32.5	0.975	1.170	1.365	1.560	1.755	1.950	2.145	2.340	2.535	2.730	2.925	3.120	3.315	3.510	3.705	3.900
35	1.050	1.260	1.470	1.680	1.890	2.100	2.310	2.520	2.730	2.940	3.150	3.360	3.570	3.780	3.990	4.200
37.5	1.125	1.350	1.575	1.800	2.025	2.250	2.475	2.700	2.925	3.150	3.375	3.600	3.825	4.050	4.275	4.500
40	1.200	1.440	1.680	1.920	2.160	2.400	2.640	2.880	3.120	3.360	3.600	3.840	4.080	4.320	4.560	4.800
42.5	1.275	1.530	1.785	2.040	2.295	2.550	2.805	3.060	3.315	3.570	3.825	4.080	4.335	4.590	4.845	5.100

Training for patients receiving continuous intravenous infusion with an external ambulatory pump

The clinical team responsible for the therapy must ensure that the patient is fully trained and competent to use the chosen infusion device. A period of personal instruction and supervision should continue until the patient is judged competent to change infusions, alter flow rates/doses as instructed, and be able to deal with common device alarms. Patients must be trained in proper aseptic technique when

preparing the treprostinil infusion reservoir and priming the infusion delivery tubing and connection. Written guidance, either from the pump manufacturer or specifically tailored advice by the prescribing physician, must be made available to the patient. This would include the required normal drug delivery actions, advice on how to manage occlusions and other pump alarms, and details of whom to contact in an emergency.

Minimising the risk of catheter related blood stream infections when using an external ambulatory pump

Particular attention must be given to the following to help minimise the risk of catheter related blood stream infections in patients that are receiving treprostinil via intravenous infusion when using an external ambulatory pump (see section 4.4). This advice is in accordance with the current best practice guidelines for the prevention of catheter-related blood stream infections, and includes:

General principles

- use of a cuffed and tunnelled central venous catheter (CVC) with a minimum number of ports.
- insertion of the CVC using sterile barrier techniques.
- use of proper hand hygiene and aseptic techniques when the catheter is inserted, replaced, accessed, repaired or when the catheter insertion site is examined and/or dressed.
- a sterile gauze (replaced every two days) or sterile, transparent, semi-permeable dressing (replaced at least every seven days) should be used to cover the catheter insertion site.
- the dressing should be replaced whenever it becomes damp, loosened, or soiled or after examination of the site.
- topical antibiotic ointments or creams should not be applied, as they may promote fungal infections and antimicrobial-resistant bacteria.

Duration of use of diluted Treposuvi solution

- the maximum duration of use of the diluted product should be no more than 24 hours.

Use of in-line 0.2 micron filter

- a 0.2 micron filter must be placed between the infusion tubing and the catheter hub and replaced every 24 hours at the time of changing the infusion reservoir.

Two further recommendations, that are potentially important for the prevention of water-borne Gram negative blood stream infections, relate to management of the catheter hub. These include:

Use of a split septum closed hub system

- the use of a closed-hub system (preferably a split septum rather than a mechanical valve device), ensures that the lumen of the catheter is sealed each time the infusion system is disconnected. This prevents the risk of exposure to microbial contamination;
- the split-septum closed-hub device should be replaced every 7 days.

Infusion system luer lock inter-connections

The risk of contamination with water-borne Gram-negative organisms is likely to be increased if a luer lock inter-connection is wet at the time of exchanging either the infusion line or the closed hub
Therefore:

- swimming and submersion of the infusion system at the site of connection with the catheter hub should be discouraged.
- at the time of replacing the closed hub device there should not be any water visible in the luer-lock connection threads.
- the infusion line should only be disconnected from the closed hub device once every 24 hours at the time of replacement.

Administration by continuous intravenous infusion with a fully internal implantable pump with the intended use of intravenous administration of Treposuvi.

Treposuvi can be administered by continuous intravenous infusion via a central venous catheter using a surgically placed fully internal implantable infusion pump with the intended use of intravenous administration of Treposuvi, equipped with an alarm (integrating occlusion and low battery alert), and an internal 0.22 μm filter to limit the risk of blood stream infection. Fixed flow rate implantable pumps are available with different reservoir volume options/ models to allow the infusion of the appropriate individual doses and avoid overdose or underdose situations. The service life of the septum should be, at minimum 500 punctures for Filling port, 250 punctures for Catheter port.

Strictly refer to the pump manufacturer's manual for specific instructions regarding preparation, implantation, monitoring and refillings of the pump.

Based on the available stability experimental data it is preferable, if possible, to use higher than 0.5 mg/ml concentration to fill the reservoir of implantable pump (see Section 6.3). Full details for calculations considering weight and pump characteristics are provided in the pump manufacturer's manual.

Continuous intravenous infusion with implantable pump should be reserved for selected patients able to tolerate the procedure itself and already shown to tolerate treprostinil, who are stabilised with treprostinil infusion and who become intolerant of, non-suitable for or refuse the subcutaneous route or the intravenous external administration.

The initial dose with the implantable pump is the same as the stable dose administered with external infusion pumps at the time of transition. The implantable pump is not devised for initial dose adjustment.

The infusion pump should be implanted only by qualified physicians who are trained in the operation and use of the infusion system.

The pump should only be refilled at hospital sites by qualified health care professionals who are trained in the operation and use of the infusion system following the Manufacturer's Instruction for Use manual and who are prepared to manage the complications that could arise in case of inadvertent injection or leakage of treprostinil into the subcutaneous space surrounding the pump.

The fixed flow rate implantable infusion pumps may display deviations of the infusion rate over the course of their use. Safe clinical use of the implanted pump is assured by comparing the actual clinical flow rate as measured by health care professional familiarized with the use of pump at every refill considering residual drug volume remaining in the pump. The pump manufacturer's manual must be followed on each refill to determine appropriate action to be performed.

Patient should be informed to immediately contact the treating hospital site in case of an occlusion alarm.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pulmonary arterial hypertension related to veno-occlusive disease.
- Congestive heart failure due to severe left ventricular dysfunction.
- Severe liver impairment (Child-Pugh Class C).
- Active gastrointestinal ulcer, intracranial haemorrhage, injury or other bleeding condition.
- 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; decompensated cardiac failure if not under close medical supervision; severe arrhythmias; cerebrovascular events (e.g. transient ischaemic attack, stroke) within the last three months.

4.4 Special warnings and precautions for use

The decision to initiate therapy with treprostinil should take into consideration the high probability that a 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.

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.

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

If a patient contracts pulmonary oedema while on treprostinil, the possibility of an associated pulmonary veno-occlusive disease should be considered. The treatment should be stopped.

Obese patients (BMI greater than 30 kg/m^2) clear treprostinil more slowly.

The benefit of treprostinil subcutaneous treatment in patients with more severe pulmonary arterial hypertension (NYHA functional class IV) has not been established.

The efficacy/safety ratio of treprostinil has not been studied in pulmonary arterial hypertension associated with left-right cardiac shunt, portal hypertension, or HIV infection.

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

Caution is advised in situations, where treprostinil may increase the risk of bleeding by inhibiting platelet aggregation.

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

Co-administration of a cytochrome P450 (CYP)2C8 enzyme inhibitor (e.g. gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration. Treprostinil dose reduction should be considered (see section 4.5).

Co-administration of a CYP2C8 enzyme inducer (e.g. rifampicin) may decrease exposure to treprostinil. Decreased exposure is likely to reduce clinical effectiveness. Treprostinil dose increase should be considered (see section 4.5).

<u>Adverse events attributable to the intravenous drug delivery system</u>

Central venous catheter associated blood stream infections and sepsis have been reported in patients receiving treprostinil by intravenous infusion. These risks are attributable to the drug delivery system. A Centres for Disease Control retrospective survey of seven centres in the United States that used intravenous treprostinil with an external ambulatory pump for the treatment of PAH found an incidence rate for

catheter-related bloodstream infections of 1.10 events per 1000 catheter days. Clinicians should be aware of the range of possible Gram-negative and Gram-positive organisms that may infect patients with long-term central venous catheters. Therefore, continuous subcutaneous infusion of undiluted Treposuvi is the preferred mode of administration.

The risk of infections, including bloodstream infections, is significantly lower with the fully internal implantable pump than with the external ambulatory pump.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Associations to consider

+ Diuretics, antihypertensive agents, or other vasodilators

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

+ 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 in accordance with conventional medical practice recommendations when monitoring such treatments. The concomitant use of other platelet inhibitors should be avoided in patients taking anticoagulants. Continuous subcutaneous infusion of treprostinil had no effect on pharmacodynamics and pharmacokinetics of a single dose (25 mg) of warfarin. There are no data available on the potential interactions leading to increased risk of bleeding if treprostinil is co-prescribed with nitric oxide donors**.**

+ Furosemide

Treprostinil plasma clearance may be slightly reduced in patients treated with furosemide. This interaction is probably due to some common metabolic features shared by both compounds (carboxylate group glucuroconjugation).

+ Cytochrome P450 (CYP) 2C8 enzyme inducers/inhibitors

Gemfibrozil – Human pharmacokinetic studies with oral treprostinil diolamine indicated that co-administration of cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil doubles the exposure (both C_{max} and AUC) to treprostinil. It has not been determined if the safety and efficacy of treprostinil by the parenteral (subcutaneous or intravenous) route are altered by inhibitors of CYP2C8. If a CYP2C8 inhibitor (e.g. gemfibrozil, trimethoprim and deferasirox) is added to or subtracted from the

patient’s medications after the titration period, treprostinil dose adjustment should be considered.

Rifampicin - Human pharmacokinetic studies with oral treprostinil diolamine indicated that co-administration of the CYP2C8 enzyme inducer rifampicin decreases exposure to treprostinil (by approximately 20%). It has not been determined if the safety and efficacy of treprostinil by the parenteral (subcutaneous or intravenous) route are altered by rifampicin. If rifampicin is added to or subtracted from the patient’s medications after the titration period, treprostinil dose adjustment should be considered.

CYP2C8 inducers (e.g. phenytoin, carbamazepine, phenobarbital and St. John's Wort) may reduce the exposure to treprostinil. If a CYP2C8 inducer is added to or subtracted from the patient’s medications after the titration period, treprostinil dose adjustment should be considered.

+ Bosentan

In a human pharmacokinetic study conducted with bosentan (250 mg/day) and treprostinil diolamine (oral dose 2 mg/day), no pharmacokinetic interactions between treprostinil and bosentan were observed.

+ Sildenafil

In a human pharmacokinetic study conducted with sildenafil (60 mg/day) and treprostinil diolamine (oral dose 2 mg/day), no pharmacokinetic interactions between treprostinil and sildenafil were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

No adequate data on the use of treprostinil in pregnant women are available. Animal studies are insufficient with respect to effects on pregnancy (see section 5.3). The potential risk for humans is unknown. 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 using treprostinil should be advised to discontinue breastfeeding.

4.7 Effects on ability to drive and use machines

The initiation of treatment or dosage adjustments may be accompanied by undesirable effects such as symptomatic systemic hypotension or dizziness which may impair ability to drive and operate machinery.

4.8 Undesirable effects

Adverse reactions observed in placebo-controlled studies and post-marketing experience with treprostinil are ranked according to frequency using the following convention: 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); not known (cannot be estimated from the available data).

Tabulated list of adverse reactions

System organ class	Adverse reaction	Frequency
Nervous system disorders	Headache	Very common
	Dizziness	Common
Cardiac disorders	High output cardiac failure	Not known
Vascular disorders	Vasodilatation, flushing	Very common
	Hypotension	Common
	Bleeding event[§]	Common
	Thrombophlebitis*	Not known
Gastrointestinal disorders	Diarrhoea, nausea	Very common
	Vomiting	Common
Skin and subcutaneous tissue disorders	Rash	Very common
	Pruritus	Common
	Generalized rashes (macular or papular in nature)	Not known
Musculoskeletal and connective tissue disorders	Jaw pain	Very common
	Myalgia, arthralgia	Common
	Pain in extremity	Common
	Bone pain	Not known
General disorders and administration site conditions	Infusion site pain, infusion site reaction, bleeding or haematoma.	Very common
	Oedema	Common
Blood and lymphatic system disorders	Thrombocytopenia	Not known
Infections and infestations	Central venous catheter-associated blood stream infection, sepsis, bacteremia**	Not known
	Infusion site infection, subcutaneous infusion site abscess formation	Not known
	Cellulitis	Not known

* Cases of thrombophlebitis associated with peripheral intravenous infusion have been reported

**** Life-threatening and fatal cases have been reported**

§ See section «Description of selected adverse events»

Description of selected adverse events

Bleeding events

Bleeding events were common as expected in this patient population with a high proportion of patients treated with anticoagulants. 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 gastrointestinal haemorrhage, rectal haemorrhage, gum haemorrhage and melaena) in controlled clinical trials. There were also reports of haemoptysis, haematemesis and haematuria, but these occurred with the same or lower frequency than in the placebo group.

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 Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of overdose with treprostinil are similar to the effects likely to limit dose increases; they include flushing, headache, hypotension, nausea, vomiting, and diarrhoea. Patients experiencing symptoms of overdose should immediately reduce or discontinue 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: Platelet Aggregation Inhibitors, excluding 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.

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. The effect of treprostinil on heart rate in animals varies with the dose. No major effects on cardiac conduction have been observed.

Clinical efficacy and safety

Data on efficacy in adults with pulmonary arterial hypertension:

Studies with subcutaneously administered treprostinil

Two phase III randomised, double-blind, placebo-controlled clinical trials have been conducted with treprostinil administered by subcutaneous continuous infusion in subjects with stable pulmonary arterial hypertension. A total of 469 adults were included in the two trials: 270 presented with idiopathic or heritable pulmonary arterial hypertension (treprostinil group = 134 patients; placebo group = 136 patients), 90 patients presented with pulmonary arterial hypertension associated with connective tissue disease (mainly scleroderma) (treprostinil group = 41 patients; placebo group = 49 patients) and 109 patients presented with pulmonary arterial hypertension associated with congenital cardiopathy with left-right shunt (treprostinil = 58 patients; placebo = 51 patients). At baseline, the mean 6-minute walking test distance was 326 metres $\pm$ 5 in the group receiving treprostinil through subcutaneous infusion and 327 metres $\pm$ 6 in the group receiving placebo. The dose of both treatments being compared was progressively increased during the study according to pulmonary arterial hypertension symptoms and clinical tolerance. The mean dose achieved after 12 weeks was 9.3 ng/kg/min in the treprostinil group and 19.1 ng/kg/min in the placebo group. After 12 weeks of treatment, the mean variation in the 6-minute walk test compared to baseline, calculated on the global population from both trials, was -2 metres ± 6.61 metres in the patients receiving treprostinil and -21.8 metres ± 6.18 metres in the placebo group. These results reflected a mean treatment effect assessed by the 6-minute walk test of 19.7 metres ($p = 0.0064$) compared to placebo for the global population from both trials. Mean changes compared to baseline values in haemodynamic parameters (mean pulmonary arterial pressure (PAPm)), right atrial pressure (RAP), pulmonary vascular resistance (PVR), cardiac index (CI) and venous oxygen saturation (SvO_2) showed treprostinil to be superior to placebo. The improvement in signs and symptoms of pulmonary hypertension (syncope, dizziness, chest pain, fatigue and dyspnoea) was statistically significant ($p< 0.0001$). In addition, the Dyspnoea-Fatigue Rating and Borg Dyspnoea Score were improved in patients treated with treprostinil after 12 weeks ($p< 0.0001$). Analysis of a combined criterion associating the improvement of exercise capacity (6-minute walk test) of at least 10% compared to baseline after 12 weeks, an improvement by at least one NYHA class compared to baseline after 12 weeks and absence of deterioration in pulmonary hypertension together with lack of death reported before

week 12 for the global population of both studies showed the number of subjects responding to treprostinil to be 15.9% (37/233) while 3.4% (8/236) of subjects in the placebo group responded. Sub-group analysis of the global population showed a statistically significant treatment effect of treprostinil compared to placebo on the 6-minute walk test in the sub-population of subjects with idiopathic or heritable pulmonary arterial hypertension (p=0.043) but not in the sub-population of subjects with pulmonary arterial hypertension associated with scleroderma or congenital cardiopathy.

The effect seen on the primary endpoint (i.e., change in six-minute walk distance after 12 weeks treatment) was smaller than that seen in historical controls with bosentan, iloprost and epoprostenol.

No study directly comparing treprostinil and epoprostenol intravenous infusion has been conducted.

There are no data from clinical studies conducted with active comparator in patients with PAH.

Paediatric population

No specific study has been conducted in children with PAH.

5.2 Pharmacokinetic properties

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.

Subcutaneous and intravenous administration of treprostinil demonstrated bioequivalence at steady state at a dose of 10 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 (BMI > 30 kg/m^2).

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.

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.

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.
Drug interaction studies have been carried out with paracetamol (4 g/day) and warfarin (25 mg/day) in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. A study conducted with warfarin found no apparent pharmacodynamic nor pharmacokinetic interaction between treprostinil and warfarin.

The metabolism of treprostinil mainly involves CYP2C8.

Hepatic impairment
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).

Renal impairment:
Patients with severe renal impairment requiring dialysis (n=8), administration of a single 1 mg dose of orally administered treprostinil pre-and post-dialysis resulted in an $AUC_{0\text{-}inf}$ that was not significantly altered compared to healthy subjects.

5.3 Preclinical safety data

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 ≥ 300 ng/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 > 50 ng/kg/min.

As a continuously sufficient exposure to treprostinil has not been proven for any dosage 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. *In vitro* and *in vivo* genotoxicity studies did not show treprostinil to have any mutagenic or clastogenic effect.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate

Hydrochloric acid (for pH-adjustment)

Metacresol

Sodium hydroxide

Sodium chloride

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products, except for Sterile Water for Injection or 0.9% (w/v) Sodium Chloride for Injection (see section 6.6)

6.3 Shelf life

3 years
After first opening: 30 days at 30°C

Shelf life during continuous subcutaneous infusion
The chemical, physical and microbial in-use stability of a single container (syringe) of undiluted treprostinil administered via subcutaneous infusion could be established at 37°C as far as 14 days. Other storage times and conditions after first opening fall to the responsibility of the user.

Shelf life during continuous intravenous infusion with external ambulatory pump

The chemical, physical and microbial in-use stability of a single container (syringe) of diluted treprostinil solution administered via intravenous infusion could be established at 37°C as far as 24 h in polyvinylchloride, polypropylene and glass (concentration as low as 0.004 mg/ml). To minimise the risk of blood stream infections the maximum period for use of diluted treprostinil should not exceed 24 h. Other storage times and conditions after first opening fall to the responsibility of the user.

Shelf life during use with intravenous administration with implantable pump for the intended use of intravenous administration of Treposuvi.
Chemical, physical and microbiological in-use stability of diluted and undiluted Treposuvi solution administered by intravenous infusion has been demonstrated for up to 30 days at 37°C at concentrations as low as 0.5mg/ml in an implantable pump with titanium reservoir. Other in-use storage times and conditions are the responsibility of the user.

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

10 ml in 10 ml type I clear glass vial sealed with a rubber teflon-coated stopper and fitted with a yellow aluminium cap; each carton contains one vial.

6.6 Special precautions for disposal

Treposuvi solution should be used **undiluted**, if it is administered via continuous subcutaneous infusion (see section 4.2).

Treposuvi solution **should be** diluted with either sterile Water for Injection or 0.9% (w/v) Sodium Chloride for Injection, if it is administered via continuous intravenous infusion (see section 4.2).

Treposuvi solution **should be diluted** with 0.9% (w/v) Sodium Chloride for Injection, if administered by continuous intravenous infusion through a surgically placed implantable pump (see section 4.2).

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

7 MARKETING AUTHORISATION HOLDER

AOP Orphan Pharmaceuticals GmbH

Leopold-Ungar Platz 2

1190 Vienna

Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 21344/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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