Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Epoprostenol Drehm 500 microgram Powder and Solvent for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 531 microgram Epoprostenol Sodium, corresponding to 500 micrograms Epoprostenol.

Each vial of solvent contains 50 ml of a sterile glycine buffer solution containing approximately 55 mg sodium.

Where 1 vial with 500 microgram epoprostenol is reconstituted with 50 ml of sterile buffer, the resultant concentration is 10,000 nanograms per ml.

Excipients: contains 0.05 mmol sodium (1.15 mg) per vial.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion

White lyophilised powder cake in colourless glass-vials, and a clear, colourless solution in 50 ml glass vials.
When 500 microgram epoprostenol powder is reconstituted with 50 ml of the Glycine Buffer Diluent, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Haemodialysis
Epoprostenol Drehm is indicated for use in renal dialysis when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated.

Primary and secondary pulmonary hypertension
Epoprostenol Drehm is also indicated for the intravenous long-term treatment of primary pulmonary hypertension (PPH) in New York Heart Association (NYHA) functional Class III and Class IV patients who do not respond adequately to conventional therapy, and secondary pulmonary hypertension (SPH) in the scleroderma spectrum of diseases (SSD) due to intrinsic precapillary pulmonary vascular disease in patients with NYHA functional class III and IV.

There are limited data on long-term use.

4.2 Posology and method of administration

Epoprostenol Drehm must be reconstituted only with specific sterile diluent for Epoprostenol. For information regarding reconstitution, dilution and calculation of dose, please see section 6.6 .

After reconstitution Epoprostenol Drehm is a colourless solution, practically free of particles.

Epoprostenol Drehm is suitable for continuous infusion only, either intravascular or into the blood supplying the dialyser.

Epoprostenol Drehm is not to be used for bolus administration.

Renal Dialysis:

Adults:
The following general schedule of infusion has been found effective in adults:

Prior to dialysis: 4 nanograms/kg/min intravenously for 15 minutes.
During dialysis: 4 nanograms/kg/min into the arterial inlet of the dialyser.

The infusion should be stopped at the end of dialysis.

The recommended dose for renal dialysis should be exceeded only with appropriate patient monitoring.

Children and the elderly:
There is no specific information available on the use of Epoprostenol for renal dialysis in children or in elderly patients.

Primary and Secondary Pulmonary Hypertension:

Adults:
The following schedules have been found effective:

Short-term (acute) dose ranging:
A short-term dose-ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate.
The infusion rate is initiated at 2 nanograms/kg/min and increased by increments of 2 nanograms/kg/min every 15 minutes or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited.
If the initial infusion rate of 2 nanograms/kg/min is not well tolerated, a lower dosage has to be determined.

During acute dose ranging in clinical trials, the mean maximum tolerated dose was 8.6±0.3 nanograms/kg/min.

Long-term continuous infusion:
Long-term continuous infusion of Epoprostenol Drehm should be administered through a central venous catheter. Temporary peripheral intravenous infusions may be used until central access is established. Long-term infusions should be initiated at 4 nanograms/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is less than 5 nanograms/kg/min; the long-term infusion should be started at one-half the maximum tolerated infusion rate.

Dosage adjustments:
Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of PPH or the occurrence of adverse events due to excessive doses of Epoprostenol Drehm.
In general, the need for increases in dose from the initial long-term dose should be expected over time. Increases in dose should be considered if symptoms persist, or recur after improving.
The infusion rate should be increased by 1 to 2 nanograms/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be of at least 15 minutes.

Following establishment of a new infusion rate, the patient should be observed, and erect and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

During long-term infusion, the occurrence of dose-related pharmacological events similar to those observed during the dose-ranging period may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment.
Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of Epoprostenol Drehm or sudden large reductions in infusion rates should be avoided.

Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of Epoprostenol Drehm should be adjusted only under the direction of a physician.

Oral anticoagulation was continued in the PPH clinical trial population in addition to continuous intravenous Epoprostenol administration and was well tolerated. Concurrent oral anticoagulation is recommended.

Children:
There is limited information on the use of Epoprostenol for PPH/SPH in children.

Elderly:
There is limited information on the use of Epoprostenol in patients over 65. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

4.3 Contraindications

Epoprostenol Drehm is contraindicated in patients with known hypersensitivity to the drug.

Epoprostenol Drehm is contraindicated in patients with congestive heart failure arising from severe left ventricular dysfunction.

Epoprostenol Drehm should not be used chronically in patients who develop pulmonary oedema during dose-ranging.

4.4 Special warnings and precautions for use

Because of the high pH of the final infusion solutions, care should be taken to avoid extravasation during their administration and consequent risk of tissue damage.
Epoprostenol is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 minutes of the end of administration.

Blood pressure and heart rate should be monitored during administration of Epoprostenol.
Epoprostenol may either decrease or increase heart rate. The change is thought to depend on the concentration of epoprostenol administered. Hypotension may occur during infusions of Epoprostenol.

The effects of Epoprostenol on heart rate may be masked by concomitant use of drugs which affect cardiovascular reflexes.

If excessive hypotension occurs during administration of Epoprostenol, the dose should be reduced or the infusion discontinued. Hypotension may be profound with overdose and may result in loss of consciousness (see section 4.9).

Short-term dose-ranging with Epoprostenol must be performed in a hospital setting with adequate personnel and equipment for haemodynamic monitoring and emergency care.

Elevated serum glucose levels have been reported during infusion of Epoprostenol.

Renal Dialysis:
Epoprostenol is not a conventional anticoagulant. Epoprostenol has been successfully used instead of heparin in renal dialysis, but in a small proportion of dialyses clotting has developed in the dialysis circuit, requiring termination of dialysis.

During renal dialysis with Epoprostenol there is a need for careful haematological monitoring and it should be ensured that cardiac output is adequately maintained so that delivery of oxygen to peripheral tissues is not diminished.

Haemorrhagic complications have not been encountered with Epoprostenol but the possibility should be considered when the drug is administered to patients with spontaneous or drug-induced haemorrhagic diatheses. When Epoprostenol is used alone, measurements such as activated whole blood clotting time may not be reliable.

The hypotensive effect of Epoprostenol may be enhanced by the use of acetate buffer in the dialysis bath during renal dialysis.

Primary and Secondary Pulmonary Hypertension:
The hazards of Epoprostenol treatment are considered to outweigh the risks of the disease in patients with functional capacity of New York Heart Association (NYHA) Class I and Class II. Epoprostenol therapy should therefore not be initiated in these patients.

Epoprostenol should be used only by clinicians experienced in the diagnosis and treatment of this disorder.

Some patients with primary pulmonary hypertension have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease.

Epoprostenol is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with Epoprostenol requires commitment by the patient to sterile drug reconstitution, drug administration, care of the permanent central venous catheter, and access to intense and ongoing patient education.

Sterile technique must be adhered to in preparing the drug and in the care of the catheter.
Even brief interruptions in the delivery of Epoprostenol may result in rapid symptomatic deterioration. The decision to receive Epoprostenol for PPH and SPH should be based upon the understanding that there is a high likelihood that therapy with Epoprostenol will be needed for prolonged periods, possibly years, and the patient's ability to accept and care for a permanent intravenous catheter and infusion pump should be carefully considered.

The enclosed Glycine Buffer Diluent contains no preservative; consequently a vial should be used once only and then discarded.

This medicinal product contains approximately 2.43 mmol (or 56 mg) sodium after reconstitution with 50 ml of the Glycine Buffer Diluent.
To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

When Epoprostenol Drehm is administered to patients receiving concomitant anticoagulants standard anticoagulant monitoring is advisable as there may be potentiation of effect.

When NSAIDS or other drugs affecting platelets aggregation are used concomitantly, there is the potential for Epoprostenol Drehm to increase the risk of bleeding.

The vasodilator effect of Epoprostenol Drehm may augment or be augmented by concomitant use of other vasodilators.

The effects of Epoprostenol Drehm on heart-rate may be masked by concomitant use of drugs which affect cardiovascular reflexes.

Epoprostenol Drehm may reduce the thrombolytic efficacy of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of epoprostenol sodium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition or postnatal development (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of Epoprostenol during pregnancy.

Lactation
It is not known whether epoprostenol is excreted in breast milk. A risk to the newborns /infants cannot be excluded. Breast-feeding should be discontinued during treatment with Epoprostenol.

Fertility
Epoprostenol had no effect on male or female fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adverse reactions are listed below by system organ class and frequency. The following terminologies have been used in order to classify the occurrence of undesirable effects

- 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)

The interpretation of adverse events during long term administration of Epoprostenol is complicated by the clinical features of the underlying disease being treated.

Infections and infestations
Very common: Sepsis, septicaemia*

Blood and lymphatic system disorders
Common: Decreased platelet count

Psychiatric disorders
Common: Anxiety, nervousness
Very Rare: Agitation

Nervous system disorders
Very Common: Headache

Cardiac disorders
Common: Tachycardia has been reported as a response to Epoprostenol at doses of 5 nanograms/kg/min and below.]
Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of Epoprostenol, greater than 5 nanograms/kg/min. Bradycardia associated with a considerable fall in systolic and diastolic blood pressure has followed i.v. administration of a dose of Epoprostenol equivalent to 30 nanograms/kg/min in healthy conscious volunteers.

Vascular Disorders
Very Common: Facial flushing (seen even in the anaesthetised patient)
Very Rare: Pallor

Gastrointestinal Disorders
Very Common: Nausea, vomiting
Common: Abdominal colic, sometimes reported as abdominal discomfort
Uncommon: Dry mouth

Skin and subcutaneous tissue disorders
Very Rare: Sweating

Musculoskeletal and connective tissue disorders
Very Common: Jaw pain

General disorders and administration site conditions
Rare: Local infection*, chest pain
Very Rare: Reddening over the infusion site*, occlusion of the long i.v. catheter*, pain at the injection site*, lassitude, chest tightness

* Associated with the delivery system for epoprostenol.

4.9 Overdose

The main feature of overdose is likely to be hypotension.

In general, events seen after overdose of epoprostenol represent exaggerated pharmacological effects of the drug. If overdose occurs reduce the dose or discontinue the infusion and initiate appropriate supportive measures as necessary; for example, plasma volume expansion and/or adjustment to pump flow.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic Agents; Platelet aggregation inhibitors excl. heparin, ATC code: B01AC09

Epoprostenol Drehm is epoprostenol sodium, the monosodium salt of epoprostenol, a naturally occurring prostaglandin produced by the intima of blood vessels. Epoprostenol is the most potent inhibitor of platelet aggregation known. It is also a potent vasodilator.

Infusions of 4ng/kg/min for 30 minutes have been shown to have no significant effect on heart rate or blood pressure, although facial flushing may occur at these levels.

Renal Dialysis:
Many of the actions of epoprostenol are exerted via the stimulation of adenylate cyclase, which leads to increased intracellular levels of cyclic adenosine 3'5' monophosphate (cAMP). A sequential stimulation of adenylate cyclase, followed by activation of phosphodiesterase, has been described in human platelets. Elevated cAMP levels regulate intracellular calcium concentrations by stimulating calcium removal, and this platelet aggregation is ultimately inhibited by the reduction of cytoplasmic calcium, upon which platelet shape change, aggregation and the release reaction depend.

The effect of epoprostenol on platelet aggregation is dose-related when between 2 and 16 ng/kg/min is administered intravenously, and significant inhibition of aggregation induced by adenosine diphosphate is observed at doses 4ng/kg/min and above.

Effects on platelets have been found to disappear within 2 hours of discontinuing the infusion, and haemodynamic changes due to epoprostenol to return to baseline within 10 minutes of termination of 60-minute infusions at 1−16 ng/kg/min.

Higher doses of epoprostenol sodium (20 nanograms/kg/min) disperse circulating platelet aggregates and increase by up to two fold the cutaneous bleeding time.

Epoprostenol potentates the anticoagulant activity of heparin by approximately 50%, possibly reducing the release of heparin neutralising factor.

Primary and Secondary Pulmonary Hypertension:
Intravenous Epoprostenol Drehm infusions of up to 15 minutes have been found to produce dose-related increases in cardiac index (CI) and stroke volume (SV), and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR), and mean systemic arterial pressure (SAPm). The effects of Epoprostenol Drehm on mean pulmonary artery pressure (PAPm) in patients with PPH were variable and minor.

Chronic haemodynamic effects are generally similar to acute effects. During chronic infusion cardiac index (CI), stroke volume (SV) and arterial oxygen saturation are increased and mean systemic arterial pressure (SAPm), right atrial pressure, total pulmonary resistance (TPR) and systemic vascular resistance are decreased.

5.2 Pharmacokinetic properties

Intravenously administered epoprostenol sodium is rapidly distributed from blood to tissue. At normal physiological pH and temperature, it breaks down spontaneously to 6-oxo-prostaglandin F_1a, although there is some enzymatic degradation to other products. The half-life for this process in man is expected to be no more than 6 minutes, and may be as short as 2-3 minutes, as estimated from in vitro rates of degradation of epoprostenol in human whole blood.

Pharmacokinetic studies in animals have shown the whole body distribution to be 1015ml/kg, and the whole body clearance to be 4.27ml/kg/sec. Following intravenous injection of radiolabelled epoprostenol, the highest concentrations are found in the liver, kidneys and small intestine. Steady-state plasma concentrations are reached within 15 minutes and are proportional to infusion rates. Extensive clearance by the liver has been demonstrated, with approximately 80% being removed in a single pass. Urinary excretion of the metabolites of epoprostenol accounts for between 40% and 90% of the administered dose, with biliary excretion accounting for the remainder. Urinary excretion is greater than 95% complete within 25 hours of dosing. Tissue levels decline rapidly with no evidence of accumulation.

Following the administration of radiolabelled epoprostenol to humans, the urinary and faecal recoveries of radioactivity were 82% and 4% respectively. At least 16 compounds were found, 10 of which were structurally identified. Unlike many other prostaglandins, epoprostenol is not metabolised during passage through the pulmonary circulation.

Due to the chemical instability, high potency and short half-life of epoprostenol, no precise and accurate assay has been identified as appropriate for quantifying epoprostenol in biological fluids.

5.3 Preclinical safety data

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

Fertility: A study in which male and female rats were dosed subcutaneously for 74 or 63 days respectively, with 0, 10, 30 or 100mg/kg/day, showed no effects on fertility.

There was no evidence of mutagenicity in the Ames test, micronucleus assay or DNA elution.

Carcinogenicity: Oncology studies have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for infusion:
Mannitol
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)

Solvent:
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)
Water for injection

6.2 Incompatibilities

Epoprostenol Drehm must be reconstituted using only the sterile buffer provided. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Powder for solution for infusion: 3 years
Solvent: 3 years

Protect infusion bags from light during infusion.

Renal Dialysis:
When reconstituted with the Glycine Buffer Diluent and diluted with physiological saline as instructed (see 6.6, Instructions for Use/Handling, Renal Dialysis), freshly prepared Epoprostenol solutions should be used within a maximum time frame of 12 hours at 25°C.

Primary and Secondary Pulmonary Hypertension:
When reconstituted and diluted with the Glycine Buffer Diluent as instructed (see 6.6, Instructions for Use/Handling, Primary Pulmonary Hypertension), freshly prepared Epoprostenol solutions should be infused immediately. If not used immediately, in-use storage times are the responsibility of the user and should not be longer than 24 hours at 2-8°C.
Where the solution is held in an ambulatory infusion pump system, a cold pouch must be used to maintain the temperature of the solution at 2-8°C for the full administration period. Epoprostenol Drehm solution may then be used over a 24 hour period provided that the cold pouch is changed as necessary throughout the day.
Where an ambulatory cold pouch system cannot be used the maximum administration time at 25°C is 12 hours for freshly prepared solutions.

6.4 Special precautions for storage

Powder for solution for infusion:
Keep the vial in the outer carton in order to protect from light.
Keep the vial tightly closed in order to protect from moisture.
Store below 25°C

Solvent:
Keep the vial in the outer carton in order to protect from light.
Store below 25°C

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Each pack unit contains
- one vial Epoprostenol Drehm 500microgram, containing a white freeze-dried powder cake packed in a 15 ml clear glass vial Type I with grey lyo stopper and aluminium caps with blue flip-off inserts.
- one 50ml sterile Glycine buffer solution, pH 10.5 in a clear glass vial
- one single unit sterile filter device for aseptic preparation of infusion solution

6.6 Special precautions for disposal

Reconstitution and dilution:
Particular care should be taken in the preparation of the infusion and in calculating the rate of infusion. The procedure given below should be closely followed.
Reconstitution and dilution of Epoprostenol Drehm 500 microgram must be carried out using sterile techniques, immediately prior to clinical use.
Reconstitution time should be below 30 seconds.

After reconstitution Epoprostenol Drehm is a colourless solution, practically free of particles.

Renal dialysis

Reconstitution:
1. Use only the Glycine Buffer Diluent provided for reconstitution.
2. Withdraw approximately 10 ml of the Glycine Buffer Diluent into a sterile syringe, inject the contents of the syringe into the vial containing 500 micrograms freeze-dried epoprostenol and shake gently until the powder has dissolved.
3. Draw up the resulting epoprostenol solution into the syringe, re-inject it into the remaining volume of the Glycine Buffer Diluent solution and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanograms per ml epoprostenol. Only this concentrated solution is suitable for further dilution prior to use.

When 500 microgram epoprostenol powder is reconstituted with 50 ml of the Glycine Buffer Diluent, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

Dilution:
For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile physiological saline.
It may be diluted with physiological saline (0.9%), provided a ratio of 6 volumes of saline to 1 volume of concentrated solution is not exceeded; e.g. 50 ml of concentrated solution further diluted with a maximum of 300 ml saline.

Other common intravenous fluids are unsatisfactory for the dilution of the concentrated solution as the required pH is not attained. Epoprostenol solutions are less stable at low pH.

Prior to using the concentrated solution, or the diluted form, a filtration step is needed. To filter, draw the reconstituted product into a large syringe and then attach the sterile filter provided to the syringe.

Dispense the concentrated solution directly into the chosen infusion solution using firm but not excessive pressure; the typical time taken for filtration of 50 ml of concentrated solution is 70 seconds. Mix well.

The filter unit must be used once only and then discarded.

When reconstituted and diluted as directed above, epoprostenol infusion solutions have a pH of approximately 10 and will retain 90% of their initial potency for approximately 12 hours at 25°C.

CALCULATION OF INFUSION RATE:
The infusion rate may be calculated by the following formula:

$$\textit{Infusion rate (ml/min)} = \frac{\text{dosage (ng/kg/min) x bodyweight (kg)}}{\text{concentration of solution (ng/ml)}}$$

Infusion rate (ml/hr) = Infusion rate (ml/min) x 60

Infusion rate formulae - examples
When used in renal dialysis Epoprostenol Drehm 500 microgram may be administered as the concentrated solution (a) or in diluted form (b).

a. Using *concentrated solution* i.e. 10,000 ng/ml epoprostenol.

Concentration of solution = 10,000 ng/ml epoprostenol

Dosage (ng/kg/min)	**Bodyweight (kilograms)**							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
1	0.18	0.24	0.30	0.36	0.42	0.48	0.54	0.60
2	0.36	0.48	0.60	0.72	0.84	0.96	1.08	1.20
3	0.54	0.72	0.90	1.08	1.26	1.44	1.62	1.80
4	0.72	0.96	1.20	l.44	1.68	1.92	2.16	2.40
5	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00

Flow rates in ml/hr

b. Using concentrated solution, diluted:

10ml *concentrated solution* + 40 ml physiological saline (0.9%). To give a final total volume of 50 ml.
Resultant concentration = 2,000 nanograms/ml epoprostenol.

Concentration of solution = 2,000 ng/ml epoprostenol

Dosage (ng/kg/min)	**Bodyweight (kilograms)**							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
1	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00
2	1.80	2.40	3.00	3.60	4.20	4.80	5.40	6.00
3	2.70	3.60	4.50	5.40	6.30	7.20	8.10	9.00
4	3.60	4.80	6.00	7.20	8.40	9.60	10.80	12.00
5	4.50	6.00	7.50	9.00	10.50	12.00	13.50	15.00

Flow rates in ml/hr

Primary and secondary Pulmonary Hypertension
The following pack unit is available for use in the treatment of primary pulmonary hypertension:
One vial containing sterile freeze-dried epoprostenol sodium equivalent to 500 micrograms epoprostenol supplied with one 50 ml vial of sterile Glycine Buffer Diluent solution.

Initially a pack unit containing diluent buffer must be used. During chronic epoprostenol therapy the final concentration of solution may be increased by the addition of a further 500 microgram or 1.5 mg vial of freeze dried epoprostenol.

Only vials of the same amount as that included in the initial starter pack may be used to increase the final concentration of solution.

Reconstitution:
This should be carried out according to the instructions given for renal dialysis. Where a pack containing 500 microgram epoprostenol is reconstituted with 50 ml sterile diluent the resultant concentration is 10,000 nanograms per ml.

Dilution:
Epoprostenol Drehm 500 microgram may be used either as concentrated solution or in a diluted form for the treatment of PPH/SPH. Only the Glycine Buffer Diluent provided may be used for the further dilution of reconstituted Epoprostenol Drehm 500 microgram. Physiological saline must not be used when Epoprostenol Drehm 500 microgram is to be used for the treatment of primary pulmonary hypertension.

Concentrations commonly used in the treatment of primary or secondary pulmonary hypertension are as follows:

- 15,000 ng/ml – 3vials of 500 microgram epoprostenol or one vial of 1.5mg epoprostenol reconstituted and diluted to a total volume of 100ml in the Glycine Buffer Diluent.
- 10,000 ng/ml – two vials containing 500 microgram epoprostenol reconstituted and diluted to a total volume of 100ml in the Glycine Buffer Diluent.

The maximum recommended concentration for administration in primary pulmonary hypertension is 60,000ng/ml.

Epoprostenol Drehm 500 microgram must not be administered with other parenteral solutions or medications when used for primary or secondary pulmonary hypertension.

To dilute the concentrated solution, draw it up into a larger syringe and then attach the sterile filter provided to the syringe.

Dispense the concentrated solution directly into the pump cassette using firm but not excessive pressure; the typical time taken for filtration of 50 ml of concentrated solution is 70 seconds.

Remove the filter from the syringe and draw up the additional volume of The Glycine Buffer Diluent required to achieve the desired dilution.

Refit the filter to the syringe and dispense the additional buffer through this into the concentrated Epoprostenol Drehm 500 microgram solution in the cassette.

Mix well.
The filter unit must be used for the dilution of one pack only and then discarded.

The ambulatory pump used to administer Epoprostenol Drehm 500 microgram should (1) be small and lightweight, (2) be able to adjust infusion rates in ng/kg/min increments, (3) have occlusion, end of infusion, and low battery alarms, (4) be accurate to ± 6% of the programmed rate (5) be positive pressure driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver Epodrehm 500 microgram, and (6) include a cold pouch system. The reservoir should be made of polyvinyl chloride, polypropylene, or glass.
Protect infusion bags from light during infusion.

CALCULATION OF INFUSION RATE:
The infusion rate may be calculated from the formula given above for renal dialysis.
An example of a concentration commonly used in primary or secondary pulmonary hypertension is shown below.

Infusion rates for a concentration of 15,000 nanograms/ml:

Concentration of solution = 15,000 ng/ml epoprostenol

Dosage (ng/kg/min)	**Bodyweight (kilograms)**							
	30	**40**	**50**	**60**	**70**	**80**	**90**	**100**
4				1.0	1.1	1.3	1.4	1.6
6		1.0	1.2	1.4	1.7	1.9	2.2	2.4
8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2
10	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0
12	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
14	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6
16	1.9	2.6	3.2	3.8	4.5	5.1	5.8	6.4

Flow rates in ml/hr

7 MARKETING AUTHORISATION HOLDER

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