SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epoprostenol Sodium 1.5 mg Powder and Solvent for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Epoprostenol Sodium 1.5 mg Powder and Solvent for Solution for Infusion:
Each vial contains epoprostenol sodium equivalent to 1.5 mg epoprostenol.
Excipient(s) with known effect: contains 0.054 mmol sodium (1.25 mg).

Solvent for Epoprostenol Sodium 1.5 mg Powder and Solvent for Solution for Infusion:
Each vial contains 50ml sterile glycine buffer solution.
Excipient(s) with known effect: contains 1.25 mmol sodium (28,82 mg).

For the full list of excipients, see section 6.1.

One ml of reconstituted concentrate solution contains epoprostenol (as epoprostenol sodium) 30 000 nanogram.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion
- White to almost white freeze dried powder
- Clear solution (pH 10.3-10.8)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epoprostenol is indicated for:
Pulmonary Arterial Hypertension
Epoprostenol is indicated for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III-IV symptoms to improve exercise capacity (see section 5.1).
Renal Dialysis

Epoprostenol is indicated for use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated (see section 5.1).

4.2 Posology and method of administration

Posology

Epoprostenol is only indicated for continuous infusion by intravenous route.
Pulmonary Arterial Hypertension
Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.
Short-term (acute) dose ranging
This procedure should be conducted in a hospital with adequate resuscitation equipment.
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 min 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 tolerated, a lower dose which is tolerated by the patient should be identified.
Long-term continuous infusion
Long-term continuous infusion of epoprostenol 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 nanogram/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 nanogram/kg/min; the long-term infusion should be started at one-half the maximum tolerated infusion rate.
Dose adjustments
Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of pulmonary arterial hypertension or the occurrence of adverse reactions due to excessive doses of epoprostenol.
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 of pulmonary arterial hypertension 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 min. 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 reactions may occasionally resolve without dose adjustment. Dose decreases should be made gradually in 2 nanogram/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Abrupt withdrawal of epoprostenol or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effect (see section 4.4). Except in

life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of epoprostenol should be adjusted only under the direction of a physician.
Renal Dialysis
Epoprostenol is suitable for continuous infusion only, either intravascularly or into the blood supplying the dialyser.
The following schedule of infusion has been found effective in adults:
Prior to dialysis: 4 nanograms/kg/min intravenously for 15 mins
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 careful monitoring of patient blood pressure.
Elderly
There is no specific information on the use of epoprostenol in patients over 65 years for renal dialysis or pulmonary arterial hypertension. In general, dose selection for older people should be made carefully, reflecting the greater frequency of decreased hepatic, renal (in the case of pulmonary arterial hypertension) or cardiac function and of concomitant disease or other medicinal product therapy.
Paediatric population
The safety and efficacy of epoprostenol in children younger than 18 years have not yet been established.

Method of administration
Preparation of epoprostenol intravenous injectable solution
Reconstituted solutions, prepared in real time, must not be administered over more than 12 hours when they are used at room temperature (between 15°C and 25°C). They should be kept under 25°C and protected from light.
It is possible to refrigerate epoprostenol reconstituted solutions, before they are used at room temperature, ranging between 2°C and 8°C and without exceeding 40 hour storage. In this case, the solutions should not be used over more than 8 hours when administered at room temperature.
The reconstituted solution should be examined prior to administration. Its use is forbidden in the presence of a discoloration or particles.
For instructions on reconstitution and dilution of the medicinal product before administration, (see section 6.6).
Epoprostenol must not be administered as a bolus injection

4.3 Contraindications

Epoprostenol is contraindicated in patients:
- with known hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- with congestive heart failure arising from severe left ventricular dysfunction.
- Epoprostenol must 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.
Epoprostenol is a potent inhibitor of platelet aggregation, therefore, an increased risk for haemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding (see section 4.5).
If excessive hypotension occurs during administration of epoprostenol, the dose should be reduced or the infusion discontinued. Hypotension may be profound in overdose and may result in loss of consciousness (see section 4.9).
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 both the basal heart rate and the concentration of epoprostenol administered.
The effects of epoprostenol on heart rate may be masked by concomitant use of medicinal products which affect cardiovascular reflexes.
Extreme caution is advised in patients with coronary artery disease.
Elevated serum glucose levels have been reported (see section 4.8).

Pulmonary Arterial Hypertension

Some patients with pulmonary arterial hypertension have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease. Epoprostenol must not be used chronically in patients who develop pulmonary oedema during dose initiation (see section 4.3).
Abrupt withdrawal or interruption of infusion must be avoided, except in life-threatening situations. An abrupt interruption of therapy can induce a rebound of pulmonary arterial hypertension resulting in dizziness, asthenia, increased dyspnoea, and may lead to death (see section 4.2).
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 medicinal product reconstitution, medicinal product 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 medicinal product and in the care of the catheter. Even brief interruptions in the delivery of epoprostenol may result in rapid symptomatic deterioration. The decision to administer epoprostenol for pulmonary arterial hypertension should be based upon the patient's 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 i.v. catheter and infusion pump should be carefully considered.

Renal Dialysis

The hypotensive effect of epoprostenol may be enhanced by the use of acetate buffer in the dialysis bath during renal dialysis.
During renal dialysis with epoprostenol it should be ensured that the cardiac output increases more than minimally so that delivery of oxygen to peripheral tissue is not diminished.
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. When

epoprostenol is used alone, measurements such as activated whole blood clotting time may not be reliable.
Glycine buffer diluent contains no preservative; consequently a vial should be used once only and then discarded.
This medicinal product contains sodium. See section 2. When Epoprostenol 0.5 mg, powder and solvent for solution for infusion is reconstituted with 50 ml of Glycine buffer diluent the final injection contains 30.0 mg, equivalent to 1.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult..
When Epoprostenol 0.5 mg, powder and solvent for solution for infusion is reconstituted with 50 ml of Glycine buffer diluent, the final injection contains 30.07 mg, equivalent to 1.5% 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

When epoprostenol is administered to patients receiving concomitant anticoagulants standard anticoagulant monitoring is advisable as there may be potentiation of effects.
The vasodilator effects of epoprostenol may augment or be augmented by concomitant use of vasodilators.
Epoprostenol may reduce the thrombolytic effect of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.
When NSAIDs or other medicinal products affecting platelets aggregation are used concomitantly, there is the potential for epoprostenol to increase the risk of bleeding.
Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with epoprostenol, This may be clinically significant in patients prone to digoxin toxicity. Monitoring of digoxin levels is therefore advisable until digoxin levels are clinically stable in patients receiving treatment with epoprostenol and digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is a limited amount of data from the use of epoprostenol in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Given the absence of alternative medicinal products, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy.

Breast-feedingIt is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Breast-feeding should be discontinued during treatment with epoprostenol.

Fertility

There are no data on the effects of epoprostenol on fertility in humans. Reproductive studies in animals have shown no effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Pulmonary arterial hypertension and its therapeutic management may affect the ability to drive and operate machinery.

There are no data regarding the effect of epoprostenol used in renal dialysis on the ability to drive or operate machinery.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency.
Frequencies are defined as follows:
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)

Infections and Infestations
Common: Sepsis, septicaemia (mostly related to delivery system for epoprostenol)[1]

Blood and Lymphatic System Disorders
Common: Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
Not known: Splenomegaly, hypersplenism

Endocrine Disorders
Very rare: Hyperthyroidism

Psychiatric Disorders
Common: Anxiety, nervousness
Very rare: Agitation

Nervous System Disorders
Very common: Headache

Cardiac Disorders
Common: Tachycardia[2], bradycardia[3]
Not known: High output cardiac failure

Vascular Disorders
Very common: Facial flushing (seen even in the anaesthetised patient)

Common: Hypotension
Very rare: Pallor
Not known: Ascites

Respiratory, thoracic and mediastinal disorders
Not known: Pulmonary oedema

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

Skin and Subcutaneous Tissue Disorders
Common: Rash
Uncommon: Sweating

Musculoskeletal and Connective Tissue Disorders
Very common: Jaw pain
Common: Arthralgia

General Disorders and Administration Site Conditions
Very common: Pain (unspecified)
Common: Pain at the injection site*, chest pain
Rare: Local infection*
Very rare: Erythema over the infusion site*, occlusion of the long i.v. catheter*, lassitude, chest tightness

Investigations
Not known: Blood glucose increased

* Associated with the delivery system for epoprostenol.
[1] Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.
[2] Tachycardia has been reported as a response to epoprostenol at doses of 5 nanograms/kg/min and below.
[3] 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.

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

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 medicinal product (e.g. hypotension and complications of hypotension).
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
Mechanism of action
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.
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 thus platelet aggregation is ultimately inhibited by the reduction of cytoplasmic calcium, upon which platelet shape change, aggregation and the release reaction depends.
Pharmacodynamic effects
An infusion of 4 nanograms/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.
Pulmonary Arterial Hypertension
Intravenous epoprostenol 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 on mean pulmonary artery pressure (PAPm) in patients with PPH were variable and minor.
Clinical efficacy and safety
Chronic continuous infusions of epoprostenol in patients with idiopathic or heritable PAH were studied in 2 prospective, open, randomised trials of 8 and 12 weeks' duration (N=25 and N=81, respectively) comparing epoprostenol plus conventional therapy to conventional therapy alone. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are

described. The combined baseline 6-minute walk test median values for the conventional therapy group and epoprostenol plus conventional therapy group was 266 meters and 301 meters, respectively.

Improvements from baseline in cardiac index (0.33 vs. -0.12 L/min/m^2), stroke volume (6.01 vs. -1.32 mL/beat), arterial oxygen saturation (1.62 vs. -0.85%), mean pulmonary artery pressure (-5.39 vs. 1.45 mm Hg), mean right atrial pressure (-2.26 vs. 0.59 mm Hg), total pulmonary resistance (-4.52 vs. 1.41 Wood U), pulmonary vascular resistance (-3.60 vs. 1.27 Wood U), and systemic vascular resistance (-4.31 vs. 0.18 Wood U) were statistically different between patients who received epoprostenol chronically and those who did not. Mean systemic arterial pressure was not significantly different between the two groups (-4.33 vs. -3.05 mm Hg). These haemodynamic improvements appeared to persist when epoprostenol was administered for at least 36 months in an open, nonrandomized study.

Statistically significant improvement was observed in exercise capacity (p=0.001), as measured by the 6MWT in patients receiving continuous intravenous epoprostenol plus conventional therapy (N=52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N=54) (combined week 8 and 12 change from baseline – median: 49 vs. -4 meters; mean: 55 vs. -4 meters). Improvements were apparent as early as the first week of therapy. At the end of the treatment period in the 12 weeks study, survival was improved in NYHA functional Class III and Class IV patients. Eight of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died (p=0.003).

Chronic continuous infusions of epoprostenol in patients with PAH/SSD were studied in a prospective, open, randomised trial of 12 weeks' duration comparing epoprostenol plus conventional therapy (N = 56) to conventional therapy alone (N = 55). Except for 5 NYHA functional Class II patients, all patients were either functional Class III or Class IV. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. The primary efficacy endpoint for the study was improvement in the 6MWT. The median baseline value for the conventional therapy group and epoprostenol plus conventional therapy group was 240 meters and 270 meters, respectively. A statistically significant increase in CI, and statistically significant decreases in PAPm, RAPm, PVR, and SAPm after 12 weeks of treatment were observed in patients who received epoprostenol chronically compared to those who did not.

Over 12 weeks, a statistical difference (p<0.001) in the change from baseline for the 6MWT was observed in the group receiving epoprostenol and conventional therapy as compared to the group receiving conventional therapy alone (median: 63.5 vs. -36.0 meters; mean: 42.9 vs. -40.7 meters).

Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnoea, as measured by the Borg Dyspnea Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol and 13/48 (27%) with conventional therapy alone worsened.

No statistical difference in survival over 12 weeks was observed in PAH/SSD patients treated with epoprostenol as compared to those receiving conventional therapy alone. At the end of the treatment period, 4 of 56 (7%) patients receiving epoprostenol died, whereas 5 of 55 (9%) patients receiving conventional therapy alone died.

Renal Dialysis

The effects of epoprostenol on platelet aggregation is dose-related when between 2 and 16 nanograms/kg/min is administered intravenously, and significant inhibition of aggregation induced by adenosine diphosphate is observed at doses of 4 nanograms/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 minutes infusion at 1 to 16 nanograms/kg/min. Higher circulating doses of epoprostenol (20 nanograms/kg/min) disperse circulating platelet aggregates and increase by up to two fold the cutaneous bleeding time. Epoprostenol potentiates the anticoagulant activity of heparin by approximately 50%, possibly reducing the release of heparin neutralising factor.

Six heparin-controlled studies and five emergency studies explored the place of epoprostenol in the general management of renal dialysis, using different techniques. Primary measurements of efficacy included intradialytic removal of BUN and creatinine, intradialytic removal of fluid (ultrafiltration), and clotting within the extracorporeal circuit.

Major clotting (dialysis permanently suspended, or requiring changing of artificial kidney) occurred in approximately 9% (n=56) of all epoprostenol dialyses and in <1% (n=1) of heparin dialyses in major controlled studies and emergency studies. Most epoprostenol dialyses (67%) that required replacement of artificial kidney were completed subsequently with epoprostenol without clotting. However, 9 of 27 epoprostenol dialyses were unsuccessful following multiple attempts.

Independent of technical difficulties which occurred rarely with either treatment, major dialysis-limiting clotting did not occur in 93% of all epoprostenol dialyses and 99% of all heparin dialyses.

Minor clotting (sufficient to require intervention, but not permanently suspending dialysis or requiring changing of the artificial kidney) was reported more frequently during epoprostenol than during heparin dialyses. None of the dialyses using heparin and 5% (n=32) of dialyses using epoprostenol had minor clotting.

Visible clotting (not necessitating intervention) was reported in another 31% of epoprostenol dialyses and 5% of heparin dialyses.

To establish that renal dialysis patients at increased risk of haemorrhage bleed less frequently with epoprostenol than heparin, 2 major prospectively controlled studies were conducted. Each patient was randomly assigned to a sequence of heparin or epoprostenol dialyses and received up to 6 dialyses per entry in one study and up to 3 dialyses per entry in another study.

Bleeding risk was defined as:

- Very high risk – presence of active bleeding at the time of dialysis initiation
- High risk – having had within 3 days prior to dialysis an active bleed that stopped at the pre-dialysis phase; or having incurred surgical or traumatic wounds within 3 days prior to dialysis

Twelve patients at very high risk of haemorrhage received 35 epoprostenol dialyses and 11 patients received 28 heparin dialyses in major controlled studies. Sixteen patients received 24 epoprostenol dialyses in emergency studies.
In major controlled studies, when all dialyses were combined for each treatment (heparin or epoprostenol), more heparin patients bled during the day prior to dialysis (N=13/17 vs. 8/23), dialysis day (N=25/28 vs. 16/35) and the day following dialysis (N=16/24 vs. 5/24) than epoprostenol patients during the same time periods.
Those patients who continued to bleed were evaluated for changes in bleeding severity. Severity of bleeding in those patients was improved more frequently with epoprostenol the day prior to dialysis and on dialysis day (predialysis: N=4/8; dialysis: N=6/16) than with heparin (predialysis: N=4/13; dialysis: N=4/25). However, the reverse was observed for postdialysis days with epoprostenol (N=1/5) compared to heparin (N=8/16). Bleeding severity worsened during only 1 dialysis day with epoprostenol (N=1/16) whereas severity worsened during 5 dialysis days (N=5/25) and 2 predialysis days (N=2/13) with heparin.
Patients who did not have clear evidence of bleeding just prior to their first study dialysis, but who bled within 3 days prior were classified as high risk of haemorrhage. Nineteen patients received 51 heparin dialyses and 19 received 44 epoprostenol dialyses in major controlled studies.
When all dialyses were combined, slightly more epoprostenol patients appeared to bleed during the predialysis (N=12/25 vs. 8/32), dialysis (23/44 vs. 14/51) and postdialysis (8/34 vs. 5/44) days compared to heparin patients during the same periods.

5.2 Pharmacokinetic properties

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.

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 F1a, although there is some enzymatic degradation to other products.
The half-life for the spontaneous breakdown to 6-oxo-prostaglandin F1 alpha 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 metabolites were found, 10 of which were structurally identified. Unlike many other prostaglandins, epoprostenol is not metabolised during passage through the pulmonary circulation.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No long-term animal studies have been conducted to determine the carcinogenic potential of epoprostenol.

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

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:	2 years
Solvent:	2 years

In-use shelf life reconstituted/diluted solution for infusion:

From a physico-chemical point of view :

- *Storage / use refrigerated:* Reconstituted solutions may be kept at 2° to 8°C for no more than 48 hours
- *Storage / use at room temperature:* When administered at room temperature (up to 25°C), reconstituted solutions may be used for no longer than 12 hours.
- *Storage refrigerated, use at room temperature:* Prior to use at room temperature, constituted solutions may be stored refrigerated for no longer than 40 hours. In this case, solutions may be used for no longer than 8 hours.

From a microbiological point of view:

– The product should be used immediately.If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Powder for solution for infusion: Keep the vial in the outer carton in order to protect from light.
Solvent: Do not freeze.

For storage conditions after reconstitution / diluton of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution for infusion: 15 ml colourless glass type I vials closed with rubber stopper and aluminium/propylene cap
Solvent: 55 ml colourless glass type I vials closed with rubber stopper and aluminium/propylene cap.

Pack sizes:

- 1, 2, 3, 4, 5, 6 or 10 packs containing 1 vial with powder for solution for infusion, 1 vial with solvent and 1 filter;
- 1, 2, 3, 4, 5, 6 or 10 packs containing 1 vial with powder for solution for infusion, 2 vials with solvent and 1 filter.

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.

The stability of solutions of Epoprostenol is pH dependent. Only the solvent supplied should be used for reconstitution of freeze-dried Epoprostenol and only the recommended infusion solutions, in the stated ratio, should be used for further dilution, otherwise the required pH may not be maintained.

Reconstitution, dilution and calculation of infusion rate:

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 must be carried out under aseptic conditions, immediately prior to clinical use.

Renal dialysis

The pack suitable for use in renal dialysis contains 0.5 mg freeze-dried Epoprostenol plus 50 mL solvent.

Reconstitution:

Use only the solvent provided for reconstitution.

Withdraw approximately 10 mL of the solvent into a sterile syringe, inject it into the vial containing 0.5 mg freeze-dried Epoprostenol powder and shake gently until the powder has dissolved.

Draw up the resulting Epoprostenol solution into the syringe, re-inject it into the remaining volume of the solvent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanograms/mL Epoprostenol. Only this concentrated solution is suitable for further dilution prior to use.
When 0.5 mg Epoprostenol powder for i.v. infusion is reconstituted with 50 mL of solvent, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

Dilution:
The concentrated solution is normally further diluted before use. It may be diluted with sodium chloride 0.9% w/v solution, provided a ratio of 6 volumes of sodium chloride 0.9% w/v solution to 1 volume of concentrated solution is not exceeded e.g. 50 mL of concentrated solution further diluted with a maximum of 300 mL sodium chloride 0.9% w/v solution.
Other common i.v. fluids are unsatisfactory for the dilution of concentrated solution as the required pH is not attained. Epoprostenol solutions are less stable at low pH.
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 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 from the following formula

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

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

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

a. Using concentrated solution, i.e. 10,000 nanograms/mL Epoprostenol:

Dosage (nanograms/ 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	1.44	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. *Diluted*: A commonly used dilution is:
10 mL concentrated solution + 40 mL sodium chloride 0.9% w/v solution.
Resultant concentration = 2,000 nanograms/mL epoprostenol

Dosage (nanograms /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

For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile sodium chloride 0.9% w/v solution**.**

Pulmonary Arterial Hypertension

There are four packs available for use in the treatment of pulmonary arterial hypertension, as follows:

One vial containing sterile, freeze-dried Epoprostenol equivalent to 0.5 mg Epoprostenol, supplied with one or two 50 mL vials of solvent and a filter unit.

One vial containing sterile, freeze-dried Epoprostenol equivalent to 1.5 mg Epoprostenol, supplied with one or two 50 mL vials of solvent and a filter unit.

One vial containing sterile, freeze-dried Epoprostenol equivalent to 0.5 mg Epoprostenol supplied alone.

One vial containing sterile, freeze-dried Epoprostenol equivalent to 1.5 mg Epoprostenol supplied alone.

Initially a pack containing solvent for parenteral use must be used. During chronic Epoprostenol therapy the final concentration of solution may be increased by the addition of a further 0.5 mg 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 1.5 mg Epoprostenol is reconstituted with 50 mL solvent the resultant concentration is 30,000 nanograms/mL

Dilution:

Epoprostenol may be used either as concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only the solvent provided may be used for the further dilution of reconstituted Epoprostenol. Sodium chloride 0.9% w/v solution must not be used when Epoprostenol is to be used for the treatment of pulmonary arterial hypertension. Epoprostenol must not be administered with other parenteral solutions or medicinal products when used for pulmonary arterial 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 solvent 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.
Concentrations commonly used in the treatment pulmonary arterial hypertension are as follows:

5,000 nanograms/mL - One vial containing 0.5 mg Epoprostenol reconstituted and diluted to a total volume of 100 mL in solvent.
10,000 nanograms/mL - Two vials containing 0.5 mg Epoprostenol reconstituted and diluted to a total volume of 100 mL in solvent.
15,000 nanograms/mL - 1.5 mg Epoprostenol reconstituted and diluted to a total volume of 100mL in solvent.

Calculation of infusion rate:

The infusion rate may be calculated from the formula given above for renal dialysis. Examples for some concentrations commonly used in pulmonary arterial hypertension are shown below.

Infusion rates for a concentration of 5,000 nanogram/ml:

Example For Dosing Using a Concentration of 5,000 nanograms/mL										
Dosage (nanograms / kg/ min)	Bodyweight (kg)									
	10	20	30	40	50	60	70	80	90	100
2				1.0	1.2	1.4	1.7	1.9	2.2	2.4
4		1.0	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
6		1.4	2.2	2.9	3.6	4.3	5.0	5.8	6.5	7.2
8	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7	8.6	9.6
10	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
12	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5	13.0	14.4
14	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4	15.1	16.8
16	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4	17.3	19.2
	Flow rates in									

Infusion rates for a concentration of 15,000 nanograms/mL

Example For Dosing Using a Concentration of 15,000 nanograms/mL								
Dosage (nanograms/ kg/ min)	Bodyweight (kg)							
	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/h**							

Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of Epoprostenol.

7 MARKETING AUTHORISATION HOLDER

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