SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epoprostenol 0.5 mg Powder and Solvent for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains 0.531 mg Epoprostenol Sodium, corresponding to 0.5 mg Epoprostenol.

Each vial of solvent contains 50 ml of a sterile glycine buffer solution containing approximately 28.9 mg sodium.

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

Excipients with known effect: contains approximately 1.3 mmol (or 30 mg) sodium after reconstitution with 50 ml of the Glycine Buffer Diluent.

For the 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 30 mg

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 the 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 i.v. 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 pulmonary arterial hypertension or the occurrence of adverse reaction 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 dosage adjustment. Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 min 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 an elderly patient 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 medicine 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 further 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 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 drugs 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 edema 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, increase 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 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 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.
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

This medicinal product contains 30 mg sodium per dose, equivalent to 1.50% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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.

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

As reported with other prostaglandin analogues, Epoprostenol may reduce the thrombolytic efficacy of tissue plasminogen activator (t-PA) by increasing hepatic clearance of t-PA.

When NSAIDS or other drugs 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, which although transient, may be clinically significant in patients prone to digoxin toxicity.

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 medicines, Epoprostenol can be used in those woman who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy.

Breastfeeding
It is unknown whether epoprostenol or its metabolites is 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 (≥10%)
- Common: ≥1/100 to <1/10 (≥1% and <10%)
- Uncommon: ≥1/1,000 to <1/100 (≥0.1% and <1%)
- Rare: ≥1/10,000 to <1/1,000 (≥0.01% and <0.1%)
- Very Rare: <1/10,000 (<0.01%)

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
Psychatric Disorders	
Common	Anxiety, nervousness
Very rare	Agitation
Nervous System Disorders	
Very common	Headache
Cardiac Disorders	
Common	Tachycardia[2], bradycardia[3]
Not known	Hight 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. Website: 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 drug (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 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.

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

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.

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.
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/m2), 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 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 circulating 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.
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 is rapidly distributed from blood to tissue. At normal physiological pH and temperature, epoprostenol breaks down spontaneously to 6-oxo-prostaglandin F_1 alpha, although there is some enzymatic degradation to other products.
Following the administration of radiolabelled epoprostenol to humans, 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.
The half-life for the spontaneous breakdown to 6-oxo-prostaglandin F_1 alpha in man is expected to be no more than 6 minutes, and may be as short as 2 to 3 minutes, as estimated from *in vitro* rates of degradation of epoprostenol in human whole blood.
Following the administration of radiolabelled epoprostenol to humans, the urinary and faecal recoveries of radioactivity were 82% and 4%, respectively.

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, carcinogenic potential, 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

Epoprostenol 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: 4 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 and Secondary 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 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 0.5mg, 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 0.5 mg must be carried out using sterile techniques, immediately prior to clinical use.
Reconstitution time should be below 30 seconds.

After reconstitution Epoprostenol 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 0.5 mg 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 0.5 mg 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 30 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:

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

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

Infusion rate formulae - examples
When used in renal dialysis Epoprostenol 0.5 mg 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
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 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 0.5 mg epoprostenol is reconstituted with 50 ml sterile diluent the resultant concentration is 10,000 nanograms per ml.

Dilution:
Epoprostenol 0.5 mg 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 0.5 mg. Physiological saline must not be used when Epoprostenol 0.5 mg is to be used for the treatment of primary or secondary pulmonary hypertension.

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

- 15,000 ng/ml – 3vials of 0.5mg 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 0.5mg 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 0.5 mg 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 0.5 mg 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 0.5 mg 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 Epoprostenol 0.5 mg, 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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