Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Veletri 0.5 Milligram Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.531 mg epoprostenol sodium equivalent to 0.5 mg epoprostenol
One mL of reconstituted solution contains 0.1 mg epoprostenol (as epoprostenol sodium) (0.5 mg epoprostenol in 5 mL of solvent).

Excipient(s) with known effect: sodium, (0.03 mg for 0.5 mg/vial)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion
White to off-white powder
For the pH of the diluted solution see section 4.4

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

VELETRI is indicated for:

Pulmonary Arterial Hypertension
VELETRI 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
VELETRI 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

Pulmonary Arterial Hypertension
VELETRI is only indicated for continuous infusion by intravenous route.
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 is initiated at 2 ng/kg/min and increased by increments of 2 ng/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 ng/kg/min is not tolerated, a lower dose that is tolerated by the patient should be identified.

Long-term continuous infusion:

Long-term continuous infusion of VELETRI 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 ng/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 ng/kg/min or less, the long-term infusion should be started at 1 ng/kg/min.

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 reactions due to excessive doses of VELETRI.

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 ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be 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 ng/kg/min decrements every 15 min or longer until the dose-limiting effects resolve. Abrupt withdrawal of VELETRI or sudden large reductions in infusion rates should be avoided due to the risk of potentially fatal rebound effect (see section 4.4). Except in life-threatening situations (e.g. unconsciousness, collapse, etc.), infusion rates of VELETRI should be adjusted only under the direction of a physician.

Renal Dialysis
VELETRI 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 ng/kg/min intravenously for 15 mins
- During dialysis: 4 ng/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 VELETRI 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 VELETRI in children have not yet been established.

Method of administration

VELETRI long-term administration is administered via intravenous route through central venous catheter using an ambulatory infusion pump. The patient must be adequately trained in all aspects of care of the central venous catheter, in the aseptic preparation of the VELETRI intravenous injectable solution, and in the preparation and change of the drug delivery reservoir of the infusion pump, and the extension set.

Additional information regarding the potential suitable materials, and instructions on connecting the i.v. access systems, ambulatory pumps to be used for the administration of VELETRI are provided in section 6.6.

Reduction of the risk of catheter-related blood-stream infection

Particular attention should be given to the recommendations in section 4.4 and the following as this should help to reduce the risk of catheter-related blood-stream infections.

The care of the central venous catheter and the catheter exit site should follow established medical principles.

Only extension sets with an in-line 0.22 micron filter placed between the infusion pump and the central venous catheter must be used. It is recommended to use filters with a hydrophilic polyethersulfone membrane. The extension set and the in-line filter must be changed at least every 48 hours (see section 6.6).

Preparation of VELETRI intravenous injectable solution:
The reconstituted solution should be examined prior to further dilution. Its use is forbidden in the presence of discolouration or particles. Reconstituted solutions should be immediately further diluted to the final concentration.

For further instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

VELETRI must not be administered as a bolus injection.

4.3 Contraindications

VELETRI 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.
- VELETRI must not be used chronically in patients who develop pulmonary oedema during dose-ranging.

4.4 Special warnings and precautions for use

The pH of the diluted "ready-to-use solution" decreases with dilution, and ranges from 12.0 for a concentration of 90 000 ng/mL, 11.7 for a concentration of 45 000 ng/mL to 11.0 for a concentration of 3 000 ng/mL. Therefore, peripheral intravenous use should be restricted to short duration only, using low concentrations.

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.

VELETRI is a potent pulmonary and systemic vasodilator. The cardiovascular effects during infusion disappear within 30 min of the end of administration.

VELETRI 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 VELETRI, 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 VELETRI.

VELETRI may either decrease or increase heart rate. The change is thought to depend on both the basal heart rate and the infusion rate of VELETRI administered.

The effects of VELETRI 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).

The solvent contains no preservative; consequently a vial should be used once only and then discarded.

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. VELETRI 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).

VELETRI is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with VELETRI 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.

Aseptic conditions must be adhered to in preparing the drug and in the care of the catheter. Even brief interruptions in the delivery of VELETRI may result in rapid symptomatic deterioration. The decision to administer VELETRI for pulmonary arterial hypertension should be based upon the patient's understanding that there is a high likelihood that therapy with VELETRI 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 VELETRI may be enhanced by the use of acetate buffer in the dialysis bath during renal dialysis.

During renal dialysis with VELETRI, it should be ensured that the cardiac output increases more than minimally so that delivery of oxygen to peripheral tissue is not diminished.

VELETRI 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.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

When VELETRI is administered to patients receiving concomitant anticoagulants, standard anticoagulant monitoring is advisable.

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

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

When NSAIDs or other drugs affecting platelet aggregation are used concomitantly, there is the potential for VELETRI to increase the risk of bleeding.

Patients on digoxin may show elevations of digoxin concentrations after initiation of therapy with VELETRI, which – although transient – may be clinically significant in patients prone to digoxin toxicity.

4.6 Fertility, pregnancy and lactation

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

Breastfeeding
It is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Breastfeeding should be discontinued during treatment with VELETRI.

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 use machines.

There are no data regarding the effect of VELETRI used in renal dialysis on the ability to drive and use machines.

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 and <1/10 (≥1% and <10%); uncommon ≥1/1 000 and <1/100 (≥0.1% and <1%); rare ≥1/10 000 and <1/1 000 (≥0.01% and <0.1%); very rare <1/10 000 (<0.01%) and not known (cannot be estimated from the available data).

Infections and Infestations	
Common	Sepsis, septicaemia (mostly related to delivery system for VELETRI)[1]
Blood and Lymphatic System Disorders	
Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
Unknown	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	
Unknown	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
Not known	Urticaria
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	
Unknown	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 ng/kg/min and below.	
[3] Bradycardia, sometimes accompanied by orthostatic hypotension, has occurred in healthy volunteers at doses of epoprostenol greater than 5 ng/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 ng/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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

The main feature of overdose is likely to be hypotension.

In general, events seen after overdose of VELETRI 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
The pH value of VELETRI is higher than the pH of other epoprostenol products.

Compared to other epoprostenol diluted solutions, which are buffered with glycine, VELETRI contains l-arginine, at lower buffering capacity. This leads to a broader range of pH values of the diluted solution. The pH decreases with dilution from 12.0 at a concentration of 90,000 ng/mL, 11.7 at a concentration of 45,000 ng/mL to 11.0 at a concentration of 3,000 ng/mL.

The studies described below under subheading "Pharmacodynamic effects" refer to studies performed with a solution of epoprostenol buffered with glycine and with a pH between 10.3 and 10.8 (Flolan).

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 ng/kg/min for 30 minutes has been shown to have no significant effect on heart rate or blood pressure, although facial flushing may occur at this level.

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 idiopathic or heritable PAH were variable and minor.

Renal Dialysis
The effects 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 of 4 ng/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 ng/kg/min.

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

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

Clinical efficacy and safety
Pulmonary Arterial Hypertension

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 (6MWT) median value 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 2 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, non-randomised 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-week 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
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 (pre-dialysis: N=4/8; dialysis: N=6/16) than with heparin (predialysis: N=4/13; dialysis: N=4/25). However, the reverse was observed for post-dialysis 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 pre-dialysis (N=12/25 vs. 8/32), dialysis (23/44 vs. 14/51) and post-dialysis (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 F1 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 F1 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 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

Sucrose
Arginine
Sodium hydroxide (for pH adjustment)

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

3 years

In use shelf life reconstituted/diluted solution for infusion:
The reconstituted solution should be immediately further diluted to the final concentration.
The diluted solution should be stored in the drug delivery reservoir in order to protect from light and can be stored for up to 8 days at 2 to 8°C.

6.4 Special precautions for storage

Do not freeze.

The reconstituted solution should be immediately further diluted to the final concentration. (see section 4.2, section 6.3 and section 6.6).
VELETRI diluted to the final concentration in the drug delivery reservoir as directed can be administered at room temperature (25°C) immediately after dilution or after storage for up to 8 days at 2 to 8°C as per the conditions of use outlined in Table 2 section 6.6. Do not expose the fully diluted solution to direct sunlight.

6.5 Nature and contents of container

Powder for solution for infusion:
10 mL colourless glass type I vial closed with a rubber stopper and an aluminium flip-off cap (with a white disc for the 0.5 mg/vial strength, and a red disc for the 1.5 mg/vial strength).

Pack presentations:
Pulmonary Arterial Hypertension
There are 2 presentations available for use in the treatment of pulmonary arterial hypertension, as follows:

- One 0.5 mg powder vial.
- One 1.5 mg powder vial.

Renal Dialysis
There is 1 presentation available for use in the treatment of renal dialysis, as follows:

- One 0.5 mg powder vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Suitable ambulatory pumps to be used for the administration of VELETRI include:

- CADD-Legacy 1
- CADD-Legacy PLUS
- CADD-Solis VIP (variable infusion profile)

Manufactured by Smiths Medical.

Pump accessories found to be compatible with the administration of VELETRI include:

- CADD disposable Medication Cassette Reservoir 50 mL; 100 mL from Smiths Medical.
- CADD extension set with in-line 0.2 micron filter (CADD extension set with male luer, 0.2 micron air-eliminating filter, clamp, and integral anti-siphon valve with male luer) from Smiths Medical.

Based on available data from inhouse testing and manufacturer accessories instructions for use, preparation and administration materials likely to be compatible include:

- Acrylic
- Acrylonitrile butadiene styrene (ABS)
- Polycarbonate
- Polyethersulfone
- Polypropylene
- Polytetrafluoroethylene (PTFE)
- Polyurethane
- Polyvinyl chloride (PVC) (plasticised with DEHP)
- Silicone

It is unknown if polyethylene terephthalate (PET) and polyethylene terephthalate glycol (PETG) are compatible with VELETRI since these materials have not been tested with VELETRI, therefore the use of these materials is not recommended.

It is recommended that the infusion pump is not carried in permanent contact with the skin in order to avoid temperature excursions of the cassette.

When connecting the extension set, ensure that there is no diluted solution in the space between the i.v. access system and the luer lock. The first drops coming from the extension set must be thoroughly wiped off before connecting the extension set to the i.v. access system.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.
The stability of solutions of VELETRI is pH dependent.
The powder for solution for infusion must be reconstituted using either Sterile Water for Injection or Sodium Chloride 0.9% Injection solution.
Further dilution should be performed with the same diluent as used for reconstitution of the sterile, lyophilised powder.

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 must be carried out under aseptic conditions.

Renal Dialysis
There is 1 pack available for use in the treatment of renal dialysis:

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

Reconstitution:
Withdraw 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection diluent into a sterile syringe, inject the contents of the syringe into the vial containing VELETRI and shake gently until the powder has dissolved. The reconstituted solution should be examined prior to further dilution. Its use is forbidden in the presence of discolouration or particles. Any unused reconstituted solution should be disposed of in accordance with local requirements.

Dilution:
The reconstituted solution should be immediately further diluted to the final concentration. Further dilution should be performed with the same diluent as used for reconstitution of the sterile, lyophilised powder.

Calculation of infusion rate:
Infusion rates may be calculated using the following formula:

$$\text{Infusion rate (mL/min)} = \frac{\text{Dosage (ng/kg/min)} \times \text{bodyweight (kg)}}{\text{Concentration of solution (ng/mL)}}$$

Infusion rate (mL/h) = Infusion rate (mL/min) × 60

A commonly used dilution is 2000 ng/mL VELETRI:

Dosage (ng/ kg/min)	Bodyweight (kg)							
	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/h**							

Pulmonary Arterial Hypertension
There are 2 packs available for use in the treatment of pulmonary arterial hypertension, as follows:

- One vial containing sterile, freeze-dried VELETRI equivalent to 0.5 mg VELETRI supplied alone.
- One vial containing sterile, freeze-dried VELETRI equivalent to 1.5 mg VELETRI supplied alone.

Reconstitution:
Withdraw 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection diluent into a sterile syringe, inject the contents of the syringe into the vial containing VELETRI and shake gently until the powder has dissolved. The reconstituted solution should be examined prior to further dilution. Its use is forbidden in the presence of discolouration or particles. Any unused reconstituted solution should be disposed of in accordance with local requirements.

Dilution:
The reconstituted solution should be immediately further diluted to the final concentration. Further dilution should be performed with the same diluent as used for reconstitution of the sterile, lyophilised powder.

VELETRI when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump. Only extension sets with an in-line 0.22 micron filter placed between the infusion pump and the catheter must be used. It is recommended to use filters with a hydrophilic polyethersulfone membrane. The extension set and the in-line filter must be changed at least every 48 hours (see section 4.4).

The vial containing 0.5 mg epoprostenol must be used for the preparation of solutions with final concentrations below 15,000 ng/mL.

Table 1 provides examples for preparing frequently used concentrations of VELETRI solutions. Each vial is for single use only.

Table 1: Frequently Used Concentrations – Examples of Reconstitution and Dilution

Final Concentration (ng/mL)	**Directions:**
3000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection. Withdraw 3 mL of the vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
5000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of either Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
10,000 ng/mL	Dissolve contents of two 0.5 mg vials, each with 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
15,000 ng/mL*	Dissolve contents of one 1.5 mg vial with 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
30,000 ng/mL*	Dissolve contents of two 1.5 mg vials, each with 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
30,000 ng/mL*	Dissolve contents of one 1.5 mg vial with 5 mL of either Sterile Water for Injection or Sodium Chloride 0.9% Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 50 mL.
* Solutions with higher final concentrations may be necessary for patients who receive long-term administration of VELETRI.	

VELETRI diluted to the final concentration in the drug delivery reservoir as directed can be administered immediately at room temperature (25°C) or, if stored, for up to 8 days at 2 to 8°C as per the conditions of use outlined in Table 2.

Table 2: Maximum Duration of Administration (hours) at Room Temperature (25°C) of Fully Diluted Solutions Stored in the Drug Delivery Reservoir

Final concentration range	**Immediate administration***	**If stored for up to 8 days at 2 to 8°C***
3000 ng/mL and <15,000 ng/mL	48 hours	24 hours
15,000 ng/mL	48 hours	48 hours

Do not expose the fully diluted solution to direct sunlight.

Calculation of infusion rate:
Infusion rates may be calculated using the following formula:

$$\text{Infusion rate (mL/min)} = \frac{\text{Dosage (ng/kg/min)} \times \text{bodyweight (kg)}}{\text{Concentration of solution (ng/mL)}}$$

Infusion rate (mL/h) = Infusion rate (mL/min) × 60

Examples for some concentrations commonly used in pulmonary arterial hypertension are shown below.

Table 3: Infusion Rates for VELETRI at a Concentration of 5000 ng/mL

Example For Dosing Using a Concentration of 5000 ng/mL										
Dosage (ng/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 **mL/h**									

Table 4: Infusion Rates for VELETRI at a Concentration of 15,000 ng/mL

Example For Dosing Using a Concentration of 15,000 ng/mL								
Dosage (ng/ 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**							

Table 5: Infusion Rates for VELETRI at a Concentration of 30,000 ng/mL

Example For Dosing Using a Concentration of 30,000 ng/mL								
Dosage (ng/kg/ min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
6						1.0	1.1	1.2
8				1.0	1.1	1.3	1.4	1.6
10			1.0	1.2	1.4	1.6	1.8	2.0
12		1.0	1.2	1.4	1.7	1.9	2.2	2.4
14		1.1	1.4	1.7	2.0	2.2	2.5	2.8
16	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2
	Flow rates in **mL/h**							

Higher dosages, and therefore, more concentrated solutions may be necessary with long-term administration of VELETRI.

7 MARKETING AUTHORISATION HOLDER

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