VELETRI®

epoprostenol (as sodium)

AUSTRALIAN PRODUCT INFORMATION

1 NAME OF THE MEDICINE

Epoprostenol (as sodium)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The reconstituted solution of VELETRI has a pH of 10.8 to 12.0 and is increasingly unstable at a lower pH. Its pKa value is 4.8.

One vial of sterile, lyophilised powder containing 0.531 mg epoprostenol sodium equivalent to 0.5 mg epoprostenol.

One vial of sterile, lyophilised powder containing 1.593 mg epoprostenol sodium equivalent to 1.5 mg epoprostenol.

Refer to Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder for injection.

VELETRI is a white to off-white powder that must be reconstituted with either sterile water for injection or with sodium chloride 0.9% solution for injection.

VELETRI for Injection is a sterile product, formulated for intravenous administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VELETRI is indicated for the long-term treatment, via continuous intravenous infusion, in WHO functional class III or class IV patients with:

- Idiopathic pulmonary arterial hypertension
- Familial pulmonary arterial hypertension
- Pulmonary arterial hypertension associated with the scleroderma spectrum of diseases.

4.2 DOSE AND METHOD OF ADMINISTRATION

General

VELETRI must be reconstituted before use. Any further dilution must be performed using the recommended solutions. Infusion sets with an in-line 0.22 micron filter must be used (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Instructions for Use/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 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.

To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets.

VELETRI is suitable for continuous intravenous infusion only. The following schedules have been found effective:

Adults

Short-term (acute) dose ranging

A short-term dose ranging procedure administered via either a peripheral or central venous line is required to determine the long-term infusion rate. The infusion is initiated at 2 ng/kg/min and increased by increments of 2 ng/kg/min every 15 minutes or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited.

Long-term continuous infusion

Long-term continuous infusion of VELETRI 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 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, then 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 (PAH) or the occurrence of adverse events 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 PAH 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 minutes. Following establishment of a new infusion rate, the patient should be observed, and erect and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

In the controlled 12-week trial in PH/SSD, for example, the dose increased from a mean starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily to a mean dose of

4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks.

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

If dose-limiting pharmacologic effects occur, then the infusion rate should be decreased to an appropriate chronic infusion rate whereby the pharmacologic effects of VELETRI are tolerated. 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.

Abrupt withdrawal of VELETRI or sudden large reductions in infusion rates must be avoided. An abrupt interruption of therapy can induce a rebound of pulmonary arterial hypertension resulting in dizziness, asthenia, increase in dyspnoea and may lead to death. Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of VELETRI should be adjusted only under the direction of a physician (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In patients receiving lung transplants, doses of epoprostenol were tapered after the initiation of cardiopulmonary bypass.

Lack of response [persistence of (New York Heart Association) NYHA class or lack of significant improvements in haemodynamic outcomes] after 3 months of epoprostenol therapy indicates poor survival and alternative options should be considered in this group of patients.

Children

There is limited information on the use of VELETRI for primary pulmonary hypertension in children.

Elderly

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

Instructions for Use/Handling

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.

<u>Reconstitution and dilution</u>

Reconstitution and dilution of VELETRI must be carried out using aseptic conditions. The powder for solution for infusion must be reconstituted using either Sterile Water for Injection or Sodium Chloride 0.9% solution for Injection. Infusion sets with an in-line 0.22 micron filter must be used.

VELETRI is stable only when reconstituted as directed using Sterile Water for Injection, or Sodium Chloride 0.9% solution for Injection. VELETRI must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration. Each vial is for single use only. Contains no antimicrobial agent, use in one patient on one occasion only. Discard any unused solution.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. If either occurs, VELETRI should not be administered. The reconstituted solution should be free from visible particles.

Use after reconstitution and immediate dilution to final concentration.

A concentration for the solution of VELETRI should be selected that is compatible with the infusion pump being used with respect to minimum and maximum flow rates and reservoir capacity. VELETRI, when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. VELETRI diluted to the final concentration in the drug delivery reservoir as directed can be stored for up to 8 days at 2° to 8°C as detailed in Tables 4 and 5.

Outlined in Table 1 are directions for preparing different concentrations of VELETRI for up to a 48-hour period. Each vial is for single use only. Contains no antimicrobial agent; use in one patient on one occasion only. Discard any unused solution.

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: Frequently used concentrations – examples of reconstitution and dilution.

Final Concentration (ng/mL)	Directions:
5,000 ng/mL	Dissolve contents of one 0.5 mg vial with 5 mL of Sterile Water for Injection, or Sodium Chloride 0.9% solution for 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 Sterile Water for Injection, or Sodium Chloride 0.9% solution for 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 Sterile Water for Injection, or Sodium Chloride 0.9% solution for Injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 mL.
* Higher concentrations may be prepared for patients who receive VELETRI long-term.	

Infusion rates may be calculated using the following formula:

$$\text{Infusion Rate (mL/h)} = \frac{[\text{Dose (ng/kg/min)} \times \text{Weight (kg)} \times 60 \text{ min/h}]}{\text{Final Concentration (ng/mL)}}$$

Examples of some concentrations commonly used in PAH are shown below in Table 2 and Table 3.

Table 2: Infusion rates for VELETRI at a concentration of 5,000 ng/mL.

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)							
	2	**4**	**6**	**8**	**10**	**12**	**14**	**16**
	Infusion Delivery Rate (mL/h)							
10	---	---	---	1.0	1.2	1.4	1.7	1.9
20	---	1.0	1.4	1.9	2.4	2.9	3.4	3.8
30	---	1.4	2.2	2.9	3.6	4.3	5.0	5.8
40	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7
50	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6
60	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5
70	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4
80	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4
90	2.2	4.3	6.5	8.6	10.8	13.0	15.1	17.3
100	2.4	4.8	7.2	9.6	12.0	14.4	16.8	19.2

Table 3: Infusion rates for VELETRI at a concentration of 15,000 ng/mL.

Patient weight (kg)	Dose or Drug Delivery Rate (ng/kg/min)						
	4	**6**	**8**	10	12	14	16
	Infusion Delivery Rate (mL/h)						
30	---	---	1.0	1.2	1.4	1.7	1.9
40	---	1.0	1.3	1.6	1.9	2.2	2.6
50	---	1.2	1.6	2.0	2.4	2.8	3.2
60	1.0	1.4	1.9	2.4	2.9	3.4	3.8
70	1.1	1.7	2.2	2.8	3.4	3.9	4.5
80	1.3	1.9	2.6	3.2	3.8	4.5	5.1
90	1.4	2.2	2.9	3.6	4.3	5.0	5.8
100	1.6	2.4	3.2	4.0	4.8	5.6	6.4

Use at room temperature (25 °C):

VELETRI solution reconstituted with 5 mL of Sterile Water for Injection or Sodium Chloride 0.9% Injection, and immediately diluted to the final concentration in the drug delivery reservoir can be administered at room temperature per the conditions of use as outlined in Table 4.

Table 4: 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*
≥ 3,000 ng/mL and <15,000 ng/mL	48 hours	24 hours
≥15,000 ng/mL	48 hours	48 hours

* Short excursions at 40°C are permitted for up to:

- 2 hours for concentrations below 15,000 ng/mL,
- 4 hours for concentrations between 15,000 ng/mL and 60,000ng/mL,
- 8 hours for concentrations above 60,000 ng/mL.

Use at higher temperatures (> 25 °C up to 30 °C):

A single reservoir of fully diluted solution of VELETRI prepared as directed above can also be administrated as outlined in Table 5.

Table 5: Maximum duration of administration (hours) at higher temperatures (> 25 °C up to 30 °C) of fully diluted solutions in the drug delivery reservoir.

Final concentration range	Immediate administration *	If stored for up to 8 days at 2 to 8 °C*
All concentrations	24 hours	24 hours

* Short excursions at 40 °C are permitted for up to:

- 2 hours for concentrations below 15,000 ng/mL,
- 4 hours for concentrations between 15,000 ng/mL and 60,000 ng/mL,
- 8 hours for concentrations above 60,000 ng/mL.

Do not freeze. Do not expose this solution to direct sunlight.

4.3 CONTRAINDICATIONS

VELETRI is contraindicated in patients with known hypersensitivity to the drug.

VELETRI is contraindicated in patients with congestive heart failure arising from severe left ventricular dysfunction, because it was found to increase mortality in such patients.

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

VELETRI should be used only by clinicians experienced in the diagnosis and treatment of PAH.

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

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

VELETRI must be reconstituted only as directed using either sterile water for injection or sodium chloride 0.9% solution for injection. It must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

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. Sterile technique must be adhered to in preparing the drug and in the care of the catheter as sepsis is a known associated risk with an indwelling central venous catheter and requires immediate access to expert medical care (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Adverse Events Attributable to the Drug Delivery System).

Chronic infusions of VELETRI must not be stopped suddenly. Even brief interruptions in the delivery of epoprostenol can lead to rapid clinical deterioration, with symptoms including dyspnoea, dizziness, and asthenia, which in some cases have been fatal. Sudden cessation of VELETRI can also lead to platelet hyperaggregability. The decision to administer VELETRI for PAH 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 intravenous catheter and infusion pump should be carefully considered. Patients must receive comprehensive training in preparation of the infusion solution and care of the catheter and pump before being allowed to self-administer VELETRI.

Because of the high pH of the final infusion solutions, care should be taken to avoid extravasation during administration and consequent risk of tissue damage.

Postmarketing cases of ascites have been reported in patients using VELETRI. The majority of cases have occurred in patients with risk factors such as right heart failure or chronic congestive hepatopathy. Clinicians should consider dose reduction or discontinuation of VELETRI therapy if ascites is not attributable to other causes.

Effects on Blood

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Unless contraindicated, anticoagulant therapy should be administered to PAH patients receiving VELETRI to reduce the risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale.

Elevated serum glucose levels have been reported.

Effects on Cardiovascular System

Extreme caution is advised in patients with coronary artery disease.

VELETRI generally increases heart rate. During or shortly after dose-ranging, some patients may experience sudden-onset bradycardia, hypotension, nausea and sweating. If this occurs, VELETRI should be immediately suspended and supportive measures instituted.

Blood pressure and heart rate should be monitored during administration of VELETRI.

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

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

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 OVERDOSE).

Use in the Elderly

There is limited information on the use of VELETRI for PAH in patients over 65 years of age.

Paediatric Use

There is limited information on the use of VELETRI for PAH in children.

Effects on Laboratory Tests

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Effects on blood.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

Epoprostenol decreased the apparent oral clearance of digoxin by 15% within two days of starting therapy. Although digoxin clearance returned to baseline levels within 90 days, prescribers should be alert to the potential for short-term elevations of digoxin concentrations after initiation of VELETRI, especially in patients prone to digoxin toxicity.

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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effect on Fertility

Fertility was not impaired in rats given epoprostenol by subcutaneous injection at doses up to 100 µg /kg/day [600 µg/m^2/day, 1.2 times the average human chronic dose (9.2 ng/kg/min or 490 µg/m^2/day, IV) based on body surface area]. However, the relevance of these animal findings in humans is unknown.

Use in Pregnancy (Pregnancy Category B1)

Reproductive studies have been performed in pregnant rats and rabbits given epoprostenol subcutaneously at doses up to 100 µg /kg/day [600 µg /m^2/day in rats, 1.2 times the average human dose, and 1100 µg /m^2/day in rabbits, 2.2 times the average human dose (9.2 ng/kg/min or 490 µg /m^2/day) based on body surface area]. These studies showed no effects of epoprostenol on pregnancy, the foetus or offspring development. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefits to the mother are considered to outweigh the possible risks to the foetus. However, the relevance of these animal findings in humans is unknown.

Use in Lactation

It is not known whether epoprostenol is excreted in human or animal milk. A risk to the breast-feeding child cannot be excluded. A decision must be made whether to discontinue/ abstain from breast-feeding or to discontinue/abstain from epoprostenol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

PAH and its therapeutic management may affect the ability to drive and operate machinery

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

During clinical trials, adverse events were classified as follows:

1. Adverse events during acute dose-ranging
2. Adverse events during chronic dosing
3. Adverse events associated with the drug delivery system

1. Adverse Events During Acute Dose-Ranging

During acute dose-ranging, epoprostenol was administered in 2 ng/kg/min increments until the patients developed symptomatic intolerance. The most common adverse events and the adverse events that limited further increases in dose were generally related to the major pharmacological effect of epoprostenol, vasodilation. Table 6 lists adverse events reported in ≥1% of 720 patients during acute dose-ranging.

Table 6: Adverse events during acute dose-ranging (frequency ≥1%) (n = 720).

52%	Flushing
44%	Headache
28%	Nausea/vomiting
14%	Hypotension
13%	Anxiety / nervousness / agitation
10%	Chest pain
6%	Dizziness
5%	Abdominal pain
4%	Bradycardia
3%	Back pain
3%	Jaw pain
2%	Dyspnoea
2%	Pain / neck pain / arthralgia
2%	Tachycardia
1%	Hypaesthesia / paraesthesia

Dose-limiting adverse events occurring in 1% or more of patients during acute dose- ranging were (in descending order of frequency): headache, nausea/vomiting, flushing, hypotension, anxiety/nervousness/agitation, chest pain, dizziness, bradycardia, abdominal pain, jaw pain, tachycardia, back pain, and dyspnoea.

2. Adverse Events During Chronic Administration

2.1. Idiopathic or Familial Pulmonary Arterial Hypertension

Interpretation of adverse events is complicated by the clinical features of PAH, which are similar to some of the pharmacologic effects of epoprostenol (e.g. dizziness, syncope). Adverse events probably related to the underlying disease include dyspnoea, fatigue, chest pain, right ventricular failure, and pallor. Several adverse events, on the other hand, can clearly be attributed to epoprostenol. These include headache, jaw pain, flushing, diarrhoea, nausea and vomiting, flu-like symptoms, allergic reactions, including anaphylaxis, and anxiety/nervousness. In an effort to separate the adverse effects of the drug from the adverse effects of the underlying disease, Table 7 lists adverse events that occurred at a rate at least 10% different in the two groups in controlled trials.

Table 7: Number (%) of patients with adverse events during chronic therapy in controlled studies. Events with ≥10% difference between epoprostenol and standard therapy.

Events more common with epoprostenol

System	Event	Epoprostenol (n=52)	Standard therapy (n=54)	Difference*
Body (General)	Jaw pain	28 (54%)	0 (0%)	54%
	Headache	43 (83%)	18 (33%)	49%
	Fever	11 (21%)	3 (6%)	16%
	Pain	15 (29%)	8 (15%)	14%
Cardiovascular	Flushing	20 (38%)	1 (2%)	37%
	Tachycardia	18 (35%)	13 (24%)	11%
Digestive	Diarrhoea	19 (37%)	3 (6%)	31%
	Nausea	35 (67%)	25 (46%)	21%
Musculoskeletal	Myalgia	23 (44%)	17 (31%)	13%
Nervous	Dizziness	43 (83%)	38 (70%)	12%

Events more common with Standard Therapy

System	Event	Epoprostenol	Standard therapy	Difference*
Cardiovascular	Syncope	7 (13%)	13 (24%)	-11%
	Shock	0 (0%)	7 (13%)	-13%
	Heart failure-right	13 (25%)	21 (39%)	-14%
	Heart failure	12 (23%)	22 (41%)	-18%
Metabolic	Cyanosis	15 (29%)	21 (39%)	-10%
Respiratory	Hypoxia	13 (25%)	20 (37%)	-12%

*Epoprostenol minus standard therapy

The following adverse events led to dose adjustment or discontinuation of epoprostenol in ≥1% of patients: dyspnoea, nausea, asthenia, flushing, headache, chest pain, diarrhoea, dizziness, vomiting, hypotension, pallor, myalgia, jaw pain, pain, and syncope.

Thrombocytopenia has been reported during uncontrolled clinical trials in patients receiving epoprostenol.

2.2. Pulmonary Arterial Hypertension Associated with Scleroderma Spectrum of Diseases

Table 8: Number (%) of patients with adverse events regardless of attribution during chronic therapy in controlled studies. Occurrences with ≥10% difference between epoprostenol and conventional therapy.

Occurrences more common with epoprostenol

System	Occurrences	Epoprostenol (n=56)	Conventional therapy (n=55)
Cardiovascular	Flushing	23%	0%
	Hypotension	13%	0%
Gastrointestinal	Anorexia	66%	47%
	Nausea/Vomiting	41%	16%
	Diarrhoea	50%	5%
Musculoskeletal	Jaw pain	75%	0%
	Pain/neck pain/arthralgia	84%	65%
Neurological	Headache	46%	5%
Skin and Appendages	Skin ulcer	39%	24%
	Eczema/rash/urticaria	25%	4%

Occurrences more common with conventional therapy

System	Occurrences	Epoprostenol	Conventional Therapy
Cardiovascular	Cyanosis	54%	80%
	Pallor	32%	53%
	Syncope	7%	20%
Gastrointestinal	Ascites	23%	33%
	Oesophageal reflux/gastritis	61%	73%
Metabolic	Weight decrease	45%	56%
Neurological	Dizziness	59%	76%
Respiratory	Hypoxia	55%	65%

Table 9: Number (%) of patients with adverse events* regardless of attribution during chronic therapy in controlled studies. Occurrences with <10% difference between epoprostenol and conventional therapy

System	Occurrences	Epoprostenol (n=56)	Conventional Therapy (n=55)
General	Asthenia	100%	98%
	Haemorrhage/haemorrhage injection site/haemorrhage rectal	11%	2%
		21%	20%

System	Occurrences	Epoprostenol (n=56)	Conventional Therapy (n=55)
	Infection/rhinitis	13%	11%
	Chills/fever/sepsis/flu-like symptoms		
Blood & Lymphatic	Thrombocytopenia	4%	0%
Cardiovascular	Heart failure/right heart failure	11%	13%
	Myocardial infarction	4%	0%
	Palpitation	63%	71%
	Shock	5%	5%
	Tachycardia	43%	42%
	Peripheral vascular disorder	96%	100%
	Vascular disorder	95%	89%
Gastrointestinal	Abdominal enlargement	4%	0%
	Abdominal pain	14%	7%
	Constipation	4%	2%
	Flatulence	5%	4%
Metabolic	Oedema/peripheral oedema/genital oedema	79%	87%
	Hypercalcaemia	48%	51%
	Hyperkalaemia	4%	0%
	Thirst	0%	4%
Musculoskeletal	Arthritis	52%	45%
	Back pain	13%	5%
	Chest pain	52%	45%
	Cramps leg	5%	7%
Respiratory	Cough increase	82%	82%
	Dyspnoea	100%	100%
	Epistaxis	9%	7%
	Pharyngitis	5%	2%
	Pleural effusion	7%	0%
	Pneumonia	5%	0%
	Pneumothorax	4%	0%
	Pulmonary oedema	4%	2%
	Respiratory disorder	7%	4%
	Sinusitis	4%	4%

System	Occurrences	Epoprostenol (n=56)	Conventional Therapy (n=55)
Neurological	Anxiety/hyperkinesia/nervousness/tremor	7%	5%
	Depression/psychotic depression	13%	4%
	Hyperaesthesia/hypaesthesia/paraesthesia	5%	0%
	Insomnia	9%	0%
	Somnolence	4%	2%
Skin & Appendages	Collagen disease	82%	84%
	Pruritus	4%	2%
	Sweat	41%	36%
Urogenital	Haematuria	5%	0%
	Urinary tract infection	7%	0%

* adverse events that occurred in at least 2 patients in either treatment group

Adverse Events Reported During Epoprostenol Use in Clinical Practice

Blood and Lymphatic: anaemia, splenomegaly, pancytopenia, bleeding at various sites.

Cardiovascular: bradycardia, hypotension and pulmonary embolism.

General: anaphylaxis, unspecified pain, arthralgia, reddening over the infusion site, occlusion of the long IV catheter, lassitude, chest tightness.

Endocrine: hyperthyroidism.

Neurological: acute confusional state.

Skin and Subcutaneous Tissue Disorders: rash and sweating.

Gastrointestinal Disorders: Diarrhoea, abdominal colic, sometimes reported as abdominal discomfort, dry mouth and hepatic failure.

Respiratory, Thoracic and Mediastinal Disorders: pulmonary oedema.

3.0 Adverse Events Attributable to the Drug Delivery System

Chronic infusions of epoprostenol are delivered using a small, portable infusion pump through an indwelling central venous catheter. During controlled PPH trials of up to 12 weeks' duration, up to 21% of patients reported a local infection and 13% of patients reported pain at the injection site. During a controlled PH/SSD trial of 12 weeks' duration, 14% of patients reported a local infection and 9% of patients reported pain at the injection site. During long-term follow-up in the clinical trial of PPH, sepsis was reported at least once in 14% of patients and occurred at a rate of 0.23 infections per patient per year in patients treated with epoprostenol. This rate was higher than reported in patients using chronic indwelling central venous catheters to administer parenteral nutrition, but lower than

reported in oncology patients using these catheters. Malfunction in the delivery system resulting in an inadvertent bolus of or a reduction in epoprostenol were associated with symptoms related to excess or insufficient epoprostenol, respectively (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) – Adverse Events During Chronic Administration).

The following serious or life-threatening adverse events related to the delivery system were reported in ≥1% of patients during chronic epoprostenol therapy: Pain at injection site, injection site reaction, sepsis and septicaemia, catheter-related infections caused by organisms not always considered pathogenic (including micrococcus), dyspnoea, pneumothorax, cellulitis, chest pain, cyanosis, haemothorax, hypotension, hypoxia, infection, pallor, procedural complication and syncope.

Post Marketing Experience

Infections and Infestations

Common	Sepsis, septicaemia (mostly related to delivery system for epoprostenol).
	Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.

Blood and Lymphatic System Disorders

Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal).
Very rare	Hypersplenism, splenomegaly

Endocrine Disorders

Very rare	Hyperthyroidism

Psychiatric Disorders

Common	Anxiety, nervousness
Very rare	Agitation

Nervous System Disorders

Very common	Headache

Cardiac Disorders

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

Vascular Disorders

Very common	Facial flushing (seen even in the anaesthetised patient)
Common	Hypotension

Very rare	Ascites, pallor

Respiratory, Thoracic and Mediastinal Disorders

Uncommon	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	Reddening over the infusion site*, occlusion of the long i.v. catheter*, lassitude, chest tightness.

* Associated with the delivery system for epoprostenol

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

In general, events seen after overdosage of epoprostenol represent exaggerated pharmacological effects of the drug (e.g. hypotension and complications of hypotension). Signs and symptoms of excessive doses of epoprostenol during clinical trials are the expected dose-limiting pharmacologic effects of epoprostenol, including flushing, headache, hypotension, tachycardia, nausea, vomiting and diarrhoea. If overdosage 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

Mechanism of action

Epoprostenol has two major pharmacological actions: (1) direct vasodilatation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation. In animals, the vasodilator effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. The effect of epoprostenol on heart rate in animals varies with dose. At low doses, there is vagally mediated bradycardia, but at higher doses, epoprostenol causes reflex tachycardia in response to direct vasodilatation and hypotension. No major effects on cardiac conduction have been observed. Additional pharmacological effects of epoprostenol in animals include bronchodilation, inhibition of gastric acid secretion, and decreased gastric emptying.

Clinical trials

Idiopathic or Familial Pulmonary Arterial Hypertension (Primary Pulmonary Hypertension)

Chronic continuous infusions of epoprostenol in patients with primary pulmonary hypertension (PPH) were studied in two prospective, open, randomised parallel controlled trials of 8 and 12 weeks' duration comparing epoprostenol plus standard therapy to standard therapy alone. Dosage of epoprostenol averaged 9.2 ng/kg per minute at study end. Standard 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 of the patients. Except for two NYHA functional Class II patients, all patients were either functional Class III or Class IV. As results are similar in the two studies, the pooled results are described below.

Haemodynamic Effects

Cardiac index (CI), stroke volume (SV), and arterial oxygen saturation were increased, and mean pulmonary artery pressure (PAPm), right atrial pressure (RAP), total pulmonary resistance (TPR), and systemic vascular resistance (SVR) were decreased in patients who received epoprostenol chronically (n = 52) compared to those who did not (n = 54). The change from baseline values is statistically significant for CI, TPR and SVR in the 8-week study, and is statistically significant for CI, SV, PAPm, mean PVR, TPR, SVR and mean systemic arterial pressure in the 12-week study. Combined results from the two controlled studies are shown in Table 10.

Table 10: Haemodynamics during chronic administration of epoprostenol in patients with PPH.

Haemodynamic Parameter	Baseline		Mean Change from Baseline at end of Treatment Period*	
	Epoprostenol (N=52)	Standard Therapy (N=54)	Epoprostenol (N=48)	Standard Therapy (N=41)
CI (L/min/m^2)	2.0	2.0	0.3**	-0.1
PAPm (mmHg)	60	60	-5**	1
PVR (Wood U)	16	17	-4**	1

Haemodynamic Parameter	Baseline		Mean Change from Baseline at end of Treatment Period*	
	Epoprostenol (N=52)	Standard Therapy (N=54)	Epoprostenol (N=48)	Standard Therapy (N=41)
SAPm (mmHg)	89	91	-4	-3
SV (mL/beat)	44	43	6**	-1
TPR (Wood U)	20	21	-5**	1

* N is the number of patients with haemodynamic data. At 8 weeks: epoprostenol = 10, standard therapy = 11. At 12 weeks: epoprostenol = 38, standard therapy = 30. ** Denotes statistically significant difference between epoprostenol and standard therapy groups.

These haemodynamic improvements appeared to persist for at least 18 months when epoprostenol was administered in an open, uncontrolled study.

Clinical Effects

In the two studies, exercise capacity, as measured by the 6-minute walk test, improved significantly in patients receiving continuous intravenous epoprostenol plus standard therapy compared to those receiving standard therapy alone. Improvements were apparent as early as the first week of therapy. In the second study, patients who received epoprostenol for 12 weeks had significant improvements ($p < 0.05$) in all 4 dimensions of the Chronic Heart Failure Questionnaire (Dyspnoea, Fatigue, Emotional Function and Mastery), as well as 2 of the 6 dimensions of the Nottingham Health Profile (Emotional Reactions and Sleep).

Survival was significantly improved in PPH patients treated with epoprostenol for 12 weeks. At the end of the treatment period, 8 of 40 patients receiving conventional therapy alone died, whereas none of the patients receiving epoprostenol in addition to conventional therapy died ($p=0.003$). The improvement in survival remained significant ($p<0.01$) when 6-minute walk was used as a covariate in the analysis due to the difference between the two groups at baseline (median of 312m and 267m for epoprostenol and conventional treatment, respectively).

In the 8-week study, although not reaching statistical significance, 90% of patients treated with epoprostenol survived, as opposed to 71% of the patients on conventional therapy alone.

In a third study, 17 patients with NYHA class III or IV PPH received continuous epoprostenol infusions for 37 to 69 months and were compared with historical controls who had received conventional therapy. The comparison was stratified according to NYHA class and transplantation status. One-, three- and five-year Kaplan-Meier survival rates in the epoprostenol-treated patients were 87%, 63% and 54%, respectively, compared with 77%, 41% and 27% in the historical controls (hazard ratio 2.9 [95%CI 1.0 to 8.0, p=0.045]).

EPITOME-1 (AC-066A401) was an exploratory, open-label, randomised, multicentre Phase IV study conducted in the USA designed to assess the safety, tolerability, and pharmacokinetics of EFI1 compared to Flolan in injectable prostanoid treatment-naïve patients with PAH. A number of protocol deviations may have affected the results. The study was conducted in a total of 30 injectable prostanoid-naïve patients randomised to either Flolan (n = 10) or EFI1 (n = 20) for a treatment period

of 28 days. Exploratory evaluation of the efficacy of EFI1 and Flolan on the basis of NYHA functional class showed that patients on both drugs were either maintained at the same functional class or improved. The results of the six-minute walk test (6MWT) were variable for the two groups and the median change from baseline after 28 days of treatment was similar in each of the treatment groups.

Blood oxygen saturation measurements were only performed in a small number of patients and after 28 days of treatment there were median decreases in both treatment groups.

EPITOME-2 (study AC-066A301) was an exploratory, prospective, multicentre, single-arm, open-label, Phase 3b study conducted in Europe and Canada, designed to evaluate cardiac haemodynamics, efficacy, safety and tolerability in PAH patients following switching from Flolan® to VELETRI. A total of 42 patients were enrolled into the study and 41 patients received study treatment and completed the study according to the protocol. Cardiac haemodynamic variables remained generally stable over the treatment period with similar mean and median values at baseline and at end of study treatment (EOT). Mean and median six minute walk distances (6MWDs) observed at baseline and at EOT were similar. At EOT, values for Borg dyspnoea scores showed a mean and median decrease from baseline. For the patients for whom a NYHA functional class evaluation was performed (n=40), the NYHA functional class remained unchanged from baseline for the majority of patients (35 patients, 87.5%) over the treatment period. One patient had an improved NYHA functional class at EOT while worsening of NYHA functional class at EOT was reported for 4 patients.

Pulmonary Arterial Hypertension (PAH) associated with scleroderma spectrum of diseases

Haemodynamic Effects:

Chronic continuous infusions of epoprostenol in patients with Pulmonary Hypertension (PH) associated with the scleroderma spectrum of diseases (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. Dosage of epoprostenol averaged 11.2 ng/kg/min at study's end. Conventional therapy varied among patients and included some or all of the following: cardiovascular medication in the majority of patients, supplemental oxygen and diuretics were taken in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. More patients took warfarin in the epoprostenol therapy group (86%) than in the conventional therapy group (67%). During the 12 week study, 53 (95%) of patients in the epoprostenol group and 41 (75%) of the conventional therapy group took at least one dose of warfarin. 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. Table 11 illustrates the treatments-related haemodynamic changes in these patients after 12 weeks of treatment.

Table 11: Haemodynamics During Chronic Administration of epoprostenol in Patients With PH/SSD.

Haemodynamic Parameter	Baseline		Mean Change from Baseline at 12 Weeks	
	Epoprostenol (N=56)	Conventional Therapy (N=55)	Epoprostenol (N=50)	Conventional Therapy (N=48)
CI (L/min/m^2)	1.9	2.2	0.5*	-0.1
PAPm (mmHg)	51	49	-5*	1
RAPm (mmHg))	13	11	-1*	1
PVR (Wood U)	14	11	-5*	1
SAPm (mmHg)	93	89	-8*	-1

*Denotes statistically significant difference between epoprostenol and conventional therapy groups (N is the number of patients with haemodynamic data). CI = cardiac index, PAPm = mean pulmonary arterial pressure, RAPm = mean right arterial pressure, PVR = pulmonary vascular resistance, SAPm = mean systemic arterial pressure.

Clinical Effects

Statistically significant improvement was observed in exercise capacity, as measured by the 6-minute walk test, in patients receiving continuous intravenous epoprostenol plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Results of the 12-week study showed that exercise capacity was improved in the 56 patients treated with epoprostenol (median distance walked in 6 minutes, 316m at 12 weeks vs 270m at Baseline), but it decreased in the 55 patients treated with conventional therapy alone (192m at 12 weeks vs. 240m at Baseline; $p<0.001$ for the comparison of the treatment groups). Increases in exercise capacity were accompanied by statistically significant improvements in dyspnoea and fatigue, as measured by the Borg Dyspnoea Index and Dyspnoea Fatigue 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. Of the patients randomised, NYHA functional class data at 12 weeks were not available for 5 patients treated with epoprostenol and 7 patients treated with conventional therapy alone.

No statistical difference in survival over 12 weeks was observed in PH/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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

At normal physiological pH and temperature, epoprostenol sodium breaks down spontaneously to 6-oxo-prostaglandin F1α, although there is some enzymatic degradation to other products.

The half-life for this process in humans 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.

Distribution

Following intravenous injection of radiolabelled epoprostenol, the highest concentrations have been found in the liver, kidneys, and small intestine. During infusions in animals, steady-state plasma concentrations of tritium-labelled epoprostenol were reached within 15 minutes and were proportional to infusion rates. Tissue levels decline rapidly with no evidence for accumulation or long-term retention of a drug-related compound.

Excretion

Urinary excretion of the metabolites of epoprostenol has been found to account for 40% of the administered dose in rats, and 90% in dogs, with biliary excretion accounting for the remainder. In both species urinary excretion was greater than 95% complete within 25 hours of dosing. In anaesthetised dogs extensive clearance by the liver has been demonstrated, with approximately 80% being removed in a single pass. Following the administration of radiolabelled epoprostenol to humans, the urinary and faecal recoveries of radioactivity were 82% and 4%, respectively. At least 16 compounds were found, 10 of which were structurally identified.

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.

Pharmacokinetic/Pharmacodynamic Studies

Two pharmacokinetic/pharmacodynamic studies (AC-066-101 and AC-066-102) were conducted; these studies were exploratory and were not designed to be bioequivalence studies.

Study AC-066-101 was a single-centre, open-label, two-period, two-treatment, cross-over, ascending dose study in healthy male subjects to assess the pharmacokinetics and pharmacodynamics of two different formulations of epoprostenol; EFI1 (the first developed formulation of VELETRI containing L-arginine and mannitol as excipients) and Flolan. Twenty healthy male subjects were enrolled in the study and 18 subjects completed the study. EFI1 and Flolan were administered in sequential infusions of 2, 4, 6, and 8 ng/kg/min for 2 h each. Due to the very short half-life of epoprostenol, the pharmacokinetic profiles of EFI 1 and Flolan were characterised via analysis of the concentration-time profiles of two primary metabolites, 6-keto-prostacyclin F1α (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-prostacyclin F1α (enzymatically formed). The plasma concentration versus time curves of EFI1 and Flolan with respect to these two primary metabolites, were essentially super-imposable.

For 6-keto-prostacyclin F1α plasma concentrations observed at 2 hours after start of each infusion step (C2, 4, 6, 8h), and the areas under the plasma concentration-time curves ($AUC_{0\text{-}2,\ 2\text{-}4,\ 4\text{-}6,\ 6\text{-}8h}$ and $AUC_{0\text{-}\infty}$) obtained after infusion of EFI1 were comparable to those obtained after infusion of Flolan®, with the 90% confidence intervals (CIs) of the geometric mean ratios falling within the range for exposure equivalence (0.80–1.25).

For 6,15-diketo-13,14-dihydro-prostacyclin F1α, plasma concentrations at 2 hours and AUC_{0-2} were not assessable after administration of EFI1 and Flolan but the other exposure parameters were comparable, with the 90% CIs of the geometric mean ratios falling within the range for exposure equivalence.

Study AC-066-102 was carried out in twenty healthy male subjects. VELETRI (containing L-arginine and sucrose as excipients) and Flolan were administered in a cross-over design in sequential infusions of 2, 4, 6, and 8 ng/kg/min for 2 h each. Overall, the comparable pharmacokinetic profiles seen in AC-066-101 were also observed with VELETRI and Flolan in AC-066-102. This resulted in comparable AUC values with 90% CIs of the geometric mean ratios contained within the 0.8-1.25 equivalence range, except for AUC_{0-2} for 6,15-diketo-13,14-dihydro-prostacyclin F1α, which was not assessable.

In addition, in both Study AC-066-101 and Study AC-066-102, the comparisons between the formulations showed comparable haemodynamic (cardiac output and heart rate), safety, and tolerability characteristics.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Epoprostenol was negative in an *in vitro* assay of gene mutation and in an *in vitro* assay of DNA damage. However, the instability of epoprostenol in solutions used for these assays makes the significance of these tests uncertain. Epoprostenol was negative in an *in vivo* assay of chromosomal damage (micronucleus tests in rats).

Carcinogenicity

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of epoprostenol.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

VELETRI contains the excipients sucrose, L-arginine, and sodium hydroxide added to adjust pH.

6.2 INCOMPATIBILITIES

Incompatabilities were either not assessed or not identified as part of the registration of this medicine. Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

For reconstituted solution, refer to section 4.2 DOSE AND METHOD OF ADMINISTRATION - Use after reconstitution and immediate dilution to final concentration.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials of VELETRI are stable until the date indicated on the package when stored below 25 °C. Protect from light. Do not freeze.

Keep unopened vial in carton until ready for use.

Each vial is for single use only. Use in one patient on one occasion only. Discard any unused solution.

For reconstituted solution, refer to section 4.2 DOSE AND METHOD OF ADMINISTRATION – Use after reconstitution and immediate dilution to final concentration.

6.5 NATURE AND CONTENTS OF CONTAINER

Sterile, lyophilised white to off-white powder in a 10 mL/20 mm Type I, clear glass borosilicate vial with a rubber stopper and flip-off cap.

The 0.5 mg vial has a white flip-off cap and the 1.5 mg vial has a red flip-off cap.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

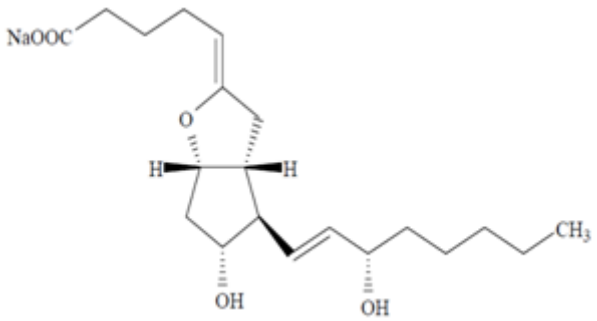
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Epoprostenol (PGI2, PGX, prostacyclin) is (5Z,9α,11α,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid, sodium salt.

Chemical structure

The structural formula of epoprostenol sodium is:



Molecular formula: C20H31NaO5
Relative molecular mass: 374.45
Epoprostenol CAS Registry Number: 35121-78-9

CAS number: 61849-14-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

SCHEDULE 4 - Prescription Only Medicine

8 SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd
Macquarie Park NSW 2113 Australia
Telephone: 1800 226 334
NZ Office: Auckland New Zealand

9 DATE OF FIRST APPROVAL

28 February 2014

10 DATE OF REVISION

28 April 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Add Urticaria as post-marketing adverse event