AUSTRALIAN PRODUCT INFORMATION

FLOLAN (epoprostenol) powder for injection

1 NAME OF THE MEDICINE

Epoprostenol sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

FLOLAN for Injection is formulated for intravenous administration. It contains the active ingredient epoprostenol (as the monosodium salt). It is a white to off-white powder that must be reconstituted with DILUENT for FLOLAN.

DILUENT for FLOLAN is a sterile buffer solution.

The reconstituted solution of FLOLAN has a pH of 11.7 to 12.3 and is increasingly unstable at a lower pH. (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Method of administration).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

FLOLAN for Injection is supplied as a sterile freeze-dried powder of epoprostenol sodium in glass vials with a DILUENT for FLOLAN.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

FLOLAN 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

FLOLAN must be reconstituted before use. Any further dilution must be performed using only the recommended solutions. The final infusion solution must be filtered with a sterile 0.22 micron or 0.20 micron filter prior to or during administration (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Method of administration).

Epoprostenol solution prepared with sterile diluent (pH 12), must not be used with any preparation or administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG) (see Section 6.2 INCOMPATIBILITIES).

FLOLAN is suitable for continuous intravenous infusion only. The following schedules have

been found effective:

Dose

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 rate 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 FLOLAN 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 PAH or the occurrence of adverse events due to excessive doses of FLOLAN.

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 of at least 15 minutes. Following establishment of a new infusion rate, the patient should be observed, and erect and supine blood pressure and heart rate monitored for several hours to ensure that the new dose is tolerated.

In the controlled 12-week trial in Pulmonary Hypertension (PH) / Scleroderma Spectrum of Diseases (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 FLOLAN 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 FLOLAN 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 dyspnoea, and may lead to death. Except in life-threatening situations (e.g. unconsciousness, collapse, etc.) infusion rates of FLOLAN 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 FLOLAN 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 FLOLAN for primary pulmonary hypertension (PPH) in children.

Elderly

There is limited information on the use of FLOLAN 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.

Method of administration

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

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

Reconstitution and dilution of FLOLAN must be carried out under aseptic conditions, ideally immediately prior to clinical use.

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

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

Epoprostenol solution prepared with sterile diluent (pH 12), must not be used with any preparation or administration materials containing PET or PETG (see Section 6.2 INCOMPATIBILITIES).

Particular care should be taken in the preparation of the infusion and in calculating the rate of infusion. The procedures given below should be closely followed.

Reconstitution

Depending on the dosage required, either 500 micrograms or 1.5 mg freeze-dried epoprostenol may be used for reconstitution with the diluent.

1. Use only the diluent provided for reconstitution.
2. Withdraw approximately 10 mL of the diluent into a sterile syringe, inject it into the vial containing freeze-dried FLOLAN and shake gently until the powder has dissolved.
3. Draw up the resulting FLOLAN solution into the syringe, re-inject it into the remaining volume of the diluent and mix thoroughly.

- Where a pack containing 500 micrograms epoprostenol is reconstituted with 50 mL sterile diluent the resultant concentration is 10,000 nanograms/mL.
- Where a pack containing 1.5 mg epoprostenol is reconstituted with 50 mL sterile diluent the resultant concentration is 30,000 nanograms/mL.

This solution is now referred to as the concentrated solution.

Only these concentrated solutions described above are suitable for further dilution with the diluent prior to use.

Dilution

FLOLAN may be used either as concentrated solution or in a diluted form for the treatment of PPH. **Only the sterile diluent provided may be used for the further dilution of reconstituted FLOLAN. Physiological saline must not be used.** FLOLAN must not be administered with other parenteral solutions or medications.

The final solution to be administered to the patient must be filtered using a 0.22 or 0.20 micron filter. Use of an in-line filter as part of the infusion set during administration is preferable. Alternatively, where in-line filtration is not possible, the final solution (either a concentrated or further diluted solution) must be filtered with the provided sterile 0.22 micron filter prior to storage in the medication cassette.

If an in-line filter has been used during administration, then the in-line filter should be discarded when the infusion set is exchanged.

If instead a syringe filter has been used during preparation, the syringe filter unit must be used only during preparation and then discarded.

To use the syringe to filter the concentrated solution and additional diluent:

Draw up the concentrated solution into a larger syringe and then attach the sterile filter provided to the syringe.

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

Remove the filter from the syringe and draw up the additional volume of diluent required to achieve the desired dilution.

Refit the filter to the syringe and dispense the additional diluent through this into the concentrated FLOLAN solution in the cassette.

Mix well.

The filter unit and any unused diluent must be discarded after completion of the dilution process.

Calculation of infusion rate

Concentrations commonly used in the treatment of pulmonary arterial hypertension are as follows:

- 15,000 ng/mL – One vial containing 1.5 mg epoprostenol reconstituted and diluted to a total volume of 100 mL in sterile diluent
- 10,000 ng/mL - See Method of administration, subheading Reconstitution. Addition of two 50 mL quantities of concentrated 10,000 ng/mL solution
- 5,000 ng/mL - One vial containing 500 micrograms epoprostenol reconstituted and diluted to a total volume of 100 mL

The infusion rate may be calculated from 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/hr) = Infusion rate (mL/min) x 60

Examples for some concentrations commonly used in PAH are shown below.

Infusion rates for a concentration of 15,000 ng/mL (15 micrograms/mL):

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

Infusion rates for a concentration of 5,000 ng/mL (5 micrograms/mL):

Dosage (ng/kg/ min)	Bodyweight (kilograms)									
	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/hr**									

4.3 CONTRAINDICATIONS

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

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

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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

Use of diluent and high pH

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

FLOLAN must be reconstituted only as directed using DILUENT for FLOLAN. It must not be reconstituted or mixed with any other parenteral medications or solutions prior to or during administration.

FLOLAN is infused continuously through a permanent indwelling central venous catheter via a small, portable infusion pump. Thus, therapy with FLOLAN 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 FLOLAN should not be stopped suddenly. Even brief interruptions in the delivery of FLOLAN can lead to rapid clinical deterioration, with symptoms including dyspnoea, dizziness, and asthenia, which in some cases has been fatal. Sudden cessation of FLOLAN can also lead to platelet hyperaggregability. The decision to administer FLOLAN for PAH should be based upon the patient's understanding that there is a high likelihood that therapy with FLOLAN 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 FLOLAN.

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.

Effects on cardiovascular system

Extreme caution is advised in patients with coronary artery disease.

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

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

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

FLOLAN 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 FLOLAN, 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).

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

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 FLOLAN to reduce the risk of pulmonary thromboembolism or systemic embolism through a patent foramen ovale.

Elevated serum glucose levels have been reported.

Use in diet

This medicinal product contains sodium, which should be taken into consideration by patients on a controlled sodium diet.

Use in the elderly

There is limited information on the use of FLOLAN in patients over 65.

Paediatric use

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

Effects on laboratory tests

See sub-section titled, “Effects on blood” above.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

FLOLAN 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 FLOLAN, especially in patients prone to digoxin toxicity.

As reported with other prostaglandin analogues, FLOLAN 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 FLOLAN to increase the risk of bleeding.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects 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

(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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

During clinical trials, adverse events were classified as follows:

- Adverse events during acute dose-ranging
- Adverse events during chronic administration
- Adverse events associated with the drug delivery system.

Adverse events during acute dose-ranging

During acute dose-ranging, FLOLAN 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 pharmacologic effect of FLOLAN, vasodilation. Table 1 lists adverse events reported in ≥1% of 720 patients during acute dose-ranging.

Table 1. 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.

Adverse events during chronic administration

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 FLOLAN (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 FLOLAN. 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 2 lists adverse events that occurred at a rate at least 10% different in the two groups in controlled trials.

Table 2. Number (%) of patients with adverse events during chronic therapy in controlled studies BW-35/56 & BW-46. 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 FLOLAN 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 FLOLAN.

Pulmonary Arterial Hypertension associated with scleroderma spectrum of diseases

Table 3. Number (%) of patients with adverse events regardless of attribution during chronic therapy in controlled studies VA1A4001. 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%
	Esophageal reflux/gastritis	61%	73%
Metabolic	Weight decrease	45%	56%
Neurological	Dizziness	59%	76%
Respiratory	Hypoxia	55%	65%

Table 4. Number (%) of patients with adverse events* regardless of attribution during chronic therapy in controlled studies VA1A4001. 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%
	Infection/rhinitis	21%	20%
	Chills/fever/sepsis/flu-like symptoms	13%	11%
Blood and 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%
	Hypercalcemia	48%	51%
	Hyperkalemia	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%
	Dyspnea	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%
Neurological	Anxiety/hyperkinesia/nervousness/		
	Tremor	7%	5%
	Depression/psychotic depression	13%	4%
	Hyperesthesia/Hypesthesia/Parathesia	5%	0%
	Insomnia	9%	0%
	Somnolence	4%	2%
Skin and appendages	Collagen Disease	82%	84%
	Pruritus	4%	2%
	Sweat	41%	36%
Urogenital	Hematuria	5%	0%
	Urinary tract infection	7%	0%

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

Adverse events reported during FLOLAN 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

Adverse events attributable to the drug delivery system

Chronic infusions of FLOLAN 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 FLOLAN. 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 FLOLAN were associated with symptoms related to excess or insufficient FLOLAN, respectively (see 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 FLOLAN 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	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 has been reported as a response to epoprostenol at doses of 5 ng/kg/min and below. 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
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

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

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.

4.9 OVERDOSE

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

For information on the management of overdose, please contact the Poisons Information Centre on 13 11 26 (Australia).

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 FLOLAN in patients with PPH were studied in two prospective, open, randomised parallel controlled trials of 8 and 12 weeks' duration comparing FLOLAN plus standard therapy to standard therapy alone (Studies BW-35/36 and BW-46). Dosage of FLOLAN was determined as described in Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 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 FLOLAN 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 5.

Table 5: Haemodynamics during chronic administration of FLOLAN in patients with PPH

Haemodynamic Parameter	Baseline		Mean change from baseline at end of treatment period *	
	FLOLAN (N=52)	Standard Therapy (N=54)	FLOLAN (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
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: FLOLAN = 10, standard therapy = 11.
At 12 weeks: FLOLAN = 38, standard therapy = 30.

** Denotes statistically significant difference between FLOLAN and standard therapy groups.

These haemodynamic improvements appeared to persist for at least 18 months when FLOLAN 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 FLOLAN 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 FLOLAN 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 FLOLAN 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 FLOLAN 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 FLOLAN and conventional treatment, respectively).

In the 8-week study, although not reaching statistical significance, 90% of patients treated with FLOLAN 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]).

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

Haemodynamic effects

Chronic continuous infusions of FLOLAN in patients with PH associated with the SSD were studied in a prospective, open, randomized trial of 12 weeks' duration comparing FLOLAN 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 FLOLAN was determined as described in the Dosage and Administration section and 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 FLOLAN therapy group (86%) than in the conventional therapy group (67%). During the 12 week study, 53 (95%) of patients in the FLOLAN 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 FLOLAN chronically compared to those who did not. Table 6 illustrates the treatments-related haemodynamic changes in these patients after 12 weeks of treatment.

Table 6. Haemodynamics During Chronic Administration of FLOLAN in Patients With PH/SSD

Haemodynamic Parameter	Baseline		Mean Change from Baseline at 12 weeks	
	FLOLAN (N= 56)	Conventional Therapy (N = 55)	FLOLAN (N = 50)	Conventional Therapy (N = 48)
CI ($L/min/m^2$)	1.9	2.2	0.5*	-0.1
PAPm (mm Hg)	51	49	-5*	1
RAPm (mm Hg)	13	11	-1*	1
PVR (Wood U)	14	11	-5*	1

SAPm (mm Hg)	93	89	-8*	-1

*Denotes statistically significant difference between FLOLAN 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, in patients receiving continuous intravenous FLOLAN 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 FLOLAN (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 240 m 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 FLOLAN compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with FLOLAN and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with FLOLAN and 13/48% (27%) with conventional therapy alone worsened. Of the patients randomized, NYHA functional class data at 12 weeks were not available for 5 patients treated with FLOLAN and 7 patients treated with conventional therapy alone.

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

5.2 PHARMACOKINETIC PROPERTIES

At normal physiological pH and temperature, epoprostenol sodium breaks down spontaneously to 6-oxo-prostaglandin $F_{1\alpha}$, 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.

Metabolism / 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.

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

FLOLAN for Injection contains the excipients glycine, sodium chloride and mannitol. Sodium hydroxide may have been added to adjust pH.

DILUENT for FLOLAN contains glycine, sodium chloride, sodium hydroxide (added to adjust pH), and Water for Injections.

6.2 INCOMPATIBILITIES

Preparation and administration materials containing PET or PETG may become damaged when used with epoprostenol solution prepared with sterile diluent (pH 12) and therefore must not be used.

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened FLOLAN vials: Store in a dry place below 25°C. Protect from light. Do not freeze.

DILUENT for FLOLAN: Store below 25°C. Protect from light. Do not freeze.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Reconstituted/diluted solutions using sterile diluent (pH 12):

Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2°C to 8°C prior to administration. Following this preparation or storage, the solution for infusion should be used within:

- 48 hours at up to 25°C or
- 36 hours at up to 30ºC or
- 24 hours at up to 35ºC or
- 12 hours at up to 40ºC

Discard any unused solution after this time.

6.5 NATURE AND CONTENTS OF CONTAINER

Freeze-dried powder

The freeze-dried powder is contained in glass vials with synthetic butyl rubber plugs and aluminium collars.

Sterile diluent (pH 12)

The sterile diluent (50 mL) is contained in plastic vials with synthetic butyl rubber plugs and aluminium collars with a purple flip-top cover.

FLOLAN for Injection is available in the following presentations:

1 vial of 500micrograms epoprostenol with 1 vial of 50 mL DILUENT and a filter.

1 vial of 500micrograms epoprostenol with 2 vials of 50 mL DILUENT and a filter.

1 vial of 1.5 mg epoprostenol with 1 vial of 50 mL DILUENT and a filter.

1 vial of 1.5 mg epoprostenol with 2 vials of 50 mL DILUENT and a filter.

* not all presentations may be marketed

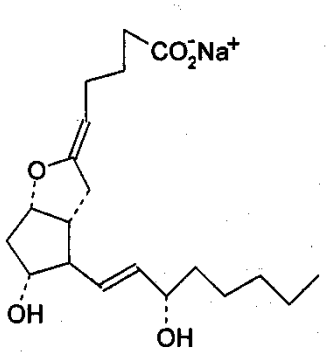
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Epoprostenol (PGI_2, PGX, prostacyclin) is (5Z,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid. The structural formula of epoprostenol sodium is:



Molecular formula: $C_{20}H_{31}NaO_5$ Relative molecular mass: 374.45

CAS number

CAS Registry Number: 61849-14-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067

9 DATE OF FIRST APPROVAL

15 February 2002

10 DATE OF REVISION OF THE TEXT

13 November 2023

Summary table of changes

Section changed	Summary of new information
6.4	Reduction of in-use shelf life

Version 13.0