

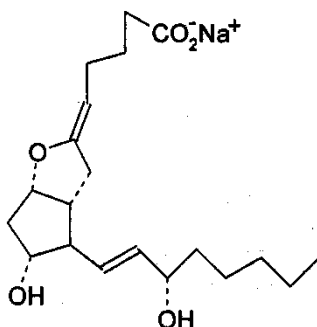
PRODUCT INFORMATION

FLOLAN[®] for Injection

NAME OF THE MEDICINE

Epoprostenol sodium

Epoprostenol (PGI₂, PGX, prostacyclin) is (5Z,9α,11α,13E,15S)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid. The structural formula of epoprostenol sodium is:



Molecular formula: C₂₀H₃₁NaO₅

Relative molecular mass: 374.45

CAS Registry Number: 61849-14-7

DESCRIPTION

FLOLAN for Injection is formulated for intravenous administration. It contains the active ingredient epoprostenol (as the monosodium salt) and the excipients glycine, sodium chloride and mannitol. Sodium hydroxide may have been added to adjust pH. It is a white to off-white powder that must be reconstituted with DILUENT for FLOLAN.

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

The reconstituted solution of FLOLAN has a pH of 10.2 to 10.8 and is increasingly unstable at a lower pH.

PHARMACOLOGY

Pharmacodynamics

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.

Pharmacokinetics

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

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.

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.

CLINICAL TRIALS

1. Idiopathic or Familial Pulmonary Arterial Hypertension (Primary Pulmonary Hypertension)

Chronic continuous infusions of FLOLAN in patients with primary pulmonary hypertension (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 DOSAGE AND 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 New York Heart Association (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.

1.1 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 1.

Table 1: 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.

1.2 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, $p=0.045$]).

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

2.1 Haemodynamic Effects:

Chronic continuous infusions of FLOLAN in patients with Pulmonary Hypertension (PH) associated with the scleroderma spectrum of diseases

(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 2 illustrates the treatments-related haemodynamic changes in these patients after 12 weeks of treatment.

Table 2. 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

2.2 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.

INDICATIONS

FLOLAN is indicated for the long-term treatment, via continuous intravenous infusion, in New York Heart Association 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

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.

PRECAUTIONS

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.

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

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.

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

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 ADVERSE EFFECTS – Adverse events Attributable to the Drug Delivery System).

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.

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

Epoprostenol is a potent inhibitor of platelet aggregation, therefore, an increased risk for haemorrhagic complications should be considered, particularly for patients with other risk factors for bleeding (see Interactions with other Medicines).

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.

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 Overdosage).

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

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.

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

Elevated serum glucose levels have been reported during infusion of FLOLAN in humans but these are not inevitable.

Effects on fertility

Fertility was not impaired in rats given epoprostenol by subcutaneous injection at doses up to 100 µg /kg/day [600 µg/m²/day, 1.2 times the average human chronic dose (9.2 ng/kg/min or 490 µg/m²/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 /m²/day in rats, 1.2 times the average human dose, and 1100 µg /m²/day in rabbits, 2.2 times the average human dose (9.2 ng/kg/min or 490 µg /m²/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. Because many drugs are excreted in human milk, caution should be exercised if FLOLAN is administered to a nursing woman.

Paediatric Use

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

Use in the Elderly

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

Carcinogenicity/Genotoxicity

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

INTERACTIONS WITH OTHER MEDICINESWhen 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.

Effects on ability to drive and use machines

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

ADVERSE EFFECTS

During clinical trials, adverse events were classified as follows:

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

1. 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 3 lists adverse events reported in $\geq 1\%$ of 720 patients during acute dose-ranging.

Table 3. Adverse events during acute dose-ranging (frequency $\geq 1\%$) (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 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 4 lists adverse events that occurred at a rate at least 10% different in the two groups in controlled trials.

Table 4. Number (%) of patients with adverse events during chronic therapy in controlled studies BW-35/56 & BW-46. Events with $\geq 10\%$ 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 $\geq 1\%$ 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.

2.2 Pulmonary Arterial Hypertension associated with scleroderma spectrum of diseases

Table 5. Number (%) of patients with adverse events regardless of attribution during chronic therapy in controlled studies VA1A4001. Occurrences with $\geq 10\%$ 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/arthritis	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 6. 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%
	Hyeresthesia/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

2.3 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 $\geq 1\%$ 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.

DOSAGE AND ADMINISTRATION

FLOLAN must be reconstituted before use. Any further dilution must be performed using only the recommended solutions (See INSTRUCTIONS FOR USE/HANDLING).

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 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 less than 5 ng/kg/min, the long-term infusion should be started at one-half the maximum tolerated infusion rate.

Dosage adjustments

Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of 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 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 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 should be avoided. Except in life-threatening situations (eg. unconsciousness, collapse, etc) infusion rates of FLOLAN should be adjusted only under the direction of a physician (see Precautions)

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

Lack of response (persistence of 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 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.

INSTRUCTIONS FOR USE/HANDLING

Glycine buffer 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.

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

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

There are six packs registered for use, as follows:

- One vial containing sterile, freeze-dried epoprostenol sodium equivalent to 500 µg epoprostenol, supplied with one 50-mL vial of sterile glycine buffer-solution and a filter unit *
- One vial containing sterile, freeze-dried epoprostenol sodium equivalent to 500 µg epoprostenol, supplied with two 50-mL vials of sterile glycine buffer-solution and a filter unit
- One vial containing sterile, freeze-dried epoprostenol sodium equivalent to 500 µg epoprostenol supplied alone *
- One vial containing sterile, freeze-dried epoprostenol sodium equivalent to 1.5 mg epoprostenol, supplied with one 50-mL vial of sterile glycine buffer-solution and a filter unit *

- One vial containing sterile, freeze-dried epoprostenol sodium equivalent to 1.5 mg epoprostenol, supplied with two 50-mL vials of sterile glycine buffer-solution and a filter unit
- One vial containing sterile, freeze-dried epoprostenol sodium equivalent to 1.5 mg epoprostenol supplied alone *

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

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

Reconstitution

Use only the sterile buffer solution provided for reconstitution.

Withdraw approximately 10 mL of the sterile buffer solution into a sterile syringe, inject it into the vial containing freeze-dried FLOLAN and shake gently until the powder has dissolved.

Draw up the resulting FLOLAN solution into the syringe, re-inject it into the remaining volume of the sterile buffer solution and mix thoroughly.

This solution is now referred to as the concentrated solution. Only this concentrated solution is suitable for further dilution 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. To dilute the concentrated solution, draw it up into a larger syringe and then attach the sterile filter provided to the syringe.

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

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

Refit the filter to the syringe and dispense the additional buffer 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.

Concentrations commonly used in the treatment of primary pulmonary 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 - Two vials containing 500 µg epoprostenol reconstituted and diluted to a total volume of 100 mL

5,000 ng/mL - One vial containing 500 µg epoprostenol reconstituted and diluted to a total volume of 100 mL

Calculation of infusion rate

The infusion rate may be calculated from the following formula:

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

$$\text{Infusion rate (mL/hr)} = \text{Infusion rate (mL/min)} \times 60$$

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

Infusion rates for a concentration of 15,000 ng/mL (15 µg/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 µg/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									

OVERDOSAGE

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 advice on management of overdosage, please contact the Poisons Information Centre on 131126

PRESENTATION AND STORAGE CONDITIONS

FLOLAN for Injection is supplied as a sterile freeze-dried powder of epoprostenol sodium in glass vials with and without DILUENT for FLOLAN in the following presentations:

1 vial of 500 µg epoprostenol only.*

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

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

1 vial of 1.5 mg epoprostenol only. *

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 currently marketed

Storage:

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.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.

Where the infusion pump allows the use of a cold pouch, Flolan solution may be used over a 24 hour period, provided that the cold pouch is changed as necessary throughout the day. Any cold pouch used must be capable of maintaining the temperature of Flolan below 15°C for the full administration period.

NAME AND ADDRESS OF SPONSOR

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Poison schedule of the medicine: S4

FLOLAN® is a registered trade mark of the GlaxoSmithKline group of companies.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):

15 February 2002

Date of most recent amendment: October 2011

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