FLOLAN

epoprostenol sodium with sterile diluent (pH 12)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials containing sterile, freeze-dried epoprostenol sodium equivalent to 0.5 mg or 1.5 mg epoprostenol.

PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Freeze-dried powder

- Vials containing sterile, freeze-dried epoprostenol sodium equivalent to 0.5 mg epoprostenol, or
- Vials containing sterile, freeze-dried epoprostenol sodium equivalent to 1.5 mg epoprostenol.

The powder is white or off-white.

Solvent

- Sterile diluent

  Vials containing 50 mL sterile diluent to reconstitute freeze-dried powder: clear, colourless solution (pH 11.7 – 12.3).

CLINICAL PARTICULARS

Indications

Renal Dialysis

FLOLAN is indicated for use in renal dialysis when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated.

Dosage and Administration

FLOLAN lyophilised powder 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 *Instructions for Use/Handling*).

FLOLAN 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 *Incompatibilities*).

Populations

- **Adults**

Renal Dialysis

FLOLAN is suitable for continuous infusion only, either intravascularly or into the blood supplying the dialyser.

The following schedule of infusion has been found effective in adults:
prior to dialysis: 4 nanograms/kg/min intravenously for 15 minutes
during dialysis: 4 nanograms/kg/min into the arterial inlet of the dialyser

The infusion should be stopped at the end of dialysis.

The recommended dose for renal dialysis should be exceeded only with careful monitoring of patient blood pressure.

- **Children**

There is no specific information on the use of *FLOLAN* for renal dialysis or pulmonary hypertension in children.

- **Elderly**

There is no specific information on the use of *FLOLAN* in patients over 65 for renal dialysis or pulmonary hypertension. In general, dose selection for an elderly patient should be made carefully, reflecting the greater frequency of decreased hepatic, renal (in the case of pulmonary hypertension) or cardiac function and of concomitant disease or other drug therapy.

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.

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

Warnings and Precautions

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

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

FLOLAN 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*).

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 *Overdose*).

Blood pressure and heart rate should be monitored during administration of *FLOLAN*. *FLOLAN* may either decrease or increase heart rate. The change is thought to depend on both the basal heart rate and the concentration of *FLOLAN* administered. 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.

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

Renal Dialysis

The hypotensive effect of *FLOLAN* may be enhanced by the use of acetate buffer in the dialysis bath during renal dialysis.

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

FLOLAN is not a conventional anticoagulant. It has been successfully used instead of heparin in renal dialysis but in a small proportion of dialyses, clotting has developed in the dialysis circuit, requiring termination of dialysis. When *FLOLAN* is used alone, measurements such as activated whole blood clotting time may not be reliable.

Interactions

When *FLOLAN* is administered to patients receiving concomitant anticoagulants, standard anticoagulant monitoring is advisable as there may be potentiation of effect.

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

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.

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

Pregnancy and Lactation

Fertility

Animal studies did not indicate harmful effects with respect to fertility. However, the relevance of these animal findings in man is unknown (see *Pre-clinical Safety Data*).

Pregnancy

Animal studies did not indicate harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. However, the relevance of these findings in man in unknown (see *Pre-clinical Safety Data*).

In the absence of adequate experience of administration of *FLOLAN* to pregnant women, the potential benefit to the mother must be weighed against the unknown risks to the foetus.

Lactation

It is unknown if epoprostenol or its metabolites are excreted in human 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 *FLOLAN* therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Effects on Ability to Drive and Use Machines

There are no data regarding the effect of *FLOLAN* used in renal dialysis on the ability to drive or operate machinery.

Adverse Reactions

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as follows: very common ≥1/10 (≥10%); common ≥1/100 and <1/10 (≥1% and <10%); uncommon ≥1/1000 and <1/100 (≥0.1% and <1%); rare ≥1/10,000 and <1/1000 (≥0.01% and <0.1%); very rare <1/10,000 (< 0.01%).

The interpretation of adverse reactions during long-term administration of epoprostenol is complicated by the clinical features of the underlying disease being treated.

Infections and Infestations

Common	Sepsis, septicaemia (mostly related to delivery system for *FLOLAN*) 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 Disorder	
Common	Anxiety, nervousness
Very rare	Agitation
Nervous System Disorders	
Very common	Headache
Cardiac Disorders	
Common	Tachycardia has been reported as a response to *FLOLAN* at doses of 5 nanograms/kg/min and below. Bradycardia, accompanied by pallor, nausea, sweating and sometimes abdominal discomfort and orthostatic hypotension, has occurred in healthy volunteers at doses of *FLOLAN* 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 *FLOLAN* 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

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 *FLOLAN*

Overdose

Symptoms and Signs

In general, events seen after overdose of *FLOLAN* represent exaggerated pharmacological effects of the drug (e.g. hypotension and complications of hypotension).

Treatment

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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

FLOLAN is the monosodium salt of epoprostenol, a naturally-occurring prostaglandin produced by the intima of blood vessels. Epoprostenol is the most potent inhibitor of platelet aggregation known. It is also a potent vasodilator.

Many of the actions of epoprostenol are exerted via the stimulation of adenylate cyclase, which leads to increased intracellular levels of cyclic adenosine 3'5' monophosphate (cAMP). A sequential stimulation of adenylate cyclase, followed by activation of phosphodiesterase, has been described in human platelets. Elevated cAMP levels regulate intracellular calcium concentrations by stimulating calcium removal, and thus platelet aggregation is ultimately inhibited by the reduction of cytoplasmic calcium, upon which platelet shape change, aggregation and the release reaction depend.

Pharmacodynamic Effects

Infusions of 4 nanograms/kg/min for 30 minutes have been shown to have no significant effect on heart rate or blood pressure, although facial flushing may occur at these levels.

Renal Dialysis

The effect of *FLOLAN* on platelet aggregation is dose-related when between 2 and 16 nanograms/kg/min is administered intravenously, and significant inhibition of aggregation induced by adenosine diphosphate is observed at doses of 4 nanograms/kg/min and above.

Effects on platelets have been found to disappear within 2 hours of discontinuing the infusion, and haemodynamic changes due to *FLOLAN* to return to baseline within 10 minutes of termination of 60-minute infusions at 1 to 16 nanograms/kg/min.

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

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

Pharmacokinetics

Due to the chemical instability, high potency and short half-life of *FLOLAN*, no precise and accurate assay has been identified for quantifying epoprostenol in biological fluids.

Distribution

Intravenously administered epoprostenol is rapidly distributed from blood to tissue.

Metabolism

At normal physiological pH and temperature, it breaks down spontaneously to 6-oxo-prostaglandin F_1alpha, although there is some enzymatic degradation to other products.

Following the administration of radiolabelled epoprostenol to humans, at least 16 metabolites were found, 10 of which were structurally identified.

Unlike many other prostaglandins, epoprostenol is not metabolised during passage through the pulmonary circulation.

Elimination

The half-life for the spontaneous breakdown to 6-oxo-prostaglandin F_1alpha in man is expected to be no more than 6 minutes, and may be as short as 2 to 3 minutes, as estimated from *in vitro* rates of degradation of epoprostenol in human whole blood.

Following the administration of radiolabelled epoprostenol to humans, the urinary and faecal recoveries of radioactivity were 82% and 4%, respectively.

Pre-clinical Safety Data

Carcinogenesis, Mutagenesis

Epoprostenol was tested *in vitro* in an Ames Salmonella assay and in an alkaline elution assay for DNA damage, and in micronucleus test on rats, at 0, 10, 20 or 40 mg/kg, in divided doses by the intraperitoneal route. There were no signs of genotoxicity in any of these three assays.

No long-term studies have been conducted in animals to determine whether epoprostenol is a potential carcinogen.

Reproductive toxicology

Epoprostenol has shown no signs of teratogenicity when administered to pregnant rabbits and rats.

A study in which male and female rats were dosed subcutaneously for 74 or 63 days respectively, with 0, 10, 30 or 100 micrograms/kg/day, showed no effects on fertility.

Studies which between them, cover all stages of the reproductive cycle, using epoprostenol doses of up to 100 micrograms/kg/day, have been conducted in rats and rabbits. No significant effects were detected on oestrus, fertility, gestation, parturition and lactation through to weaning. In litters examined pre- and post-partum, there was no evidence of foetal toxicity or teratogenicity and in maintained offspring, physical and behavioural development and fertility were normal.

Animal pharmacology

A pharmacokinetic study in rabbits showed the whole body distribution to be 1015 mL/kg, and the whole body clearance to be 4.27 mL/kg/sec. Following i.v. 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.

PHARMACEUTICAL PARTICULARS

List of Excipients

Freeze-dried powder
Glycine, sodium chloride, mannitol, sodium hydroxide BP.

Sterile diluent
Glycine, sodium chloride, sodium hydroxide, water for injection.

Incompatibilities

FLOLAN must be reconstituted using only the sterile diluent provided. Any further dilution must be performed using only the recommended solutions (see *Instructions for Use/Handling*).

FLOLAN must not be administered with other parenteral solutions or medications when used for primary pulmonary hypertension (see *Instructions for Use/Handling*).

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

Shelf Life

Unopened vials

The expiry date is indicated on the packaging.

Stability during administration

Reconstituted solutions using sterile diluent for renal dialysis.

Reconstitution and subsequent dilution should be carried out immediately prior to use (see *Instructions for Use/Handling*).

Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered for up to 12 hours at up to 25°C.

Discard any unused solution after this time.

Special Precautions for Storage

Freeze-dried powder

The storage conditions depend on the locally registered shelf-life (refer to the pack for information). Protect from light. Keep dry. Do not freeze. Under these conditions, freeze-dried *FLOLAN* in an unopened vial should not be affected by moisture present in the atmosphere.

Sterile diluent

The storage conditions depend on the locally registered shelf-life (refer to the pack for information). Do not freeze. Protect from light. Sterile diluent contains no preservative, consequently a vial should be used once only and then discarded.

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

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

Renal Dialysis

Vials containing sterile, freeze-dried epoprostenol equivalent to 0.5 mg epoprostenol, supplied with a vial containing 50 mL of sterile diluent and a filter unit.

Instructions for Use/Handling

The stability of solutions of *FLOLAN* is pH-dependent. Only the sterile 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.

FLOLAN solution prepared with sterile diluent (pH 12), must not be used with any preparation or administration materials containing PET or PETG (see *Incompatibilities*).

- **Reconstitution, dilution and calculation of infusion rate**

Reconstitution and dilution of *FLOLAN* must be carried out using aseptic technique, ideally immediately prior to clinical use.

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.

Renal Dialysis

Ideally reconstitution should be carried out immediately prior to use.

The pack suitable for use in renal dialysis contains 0.5 mg freeze-dried epoprostenol plus 50 mL sterile diluent.

Reconstitution:

1. Use only the sterile diluent provided for reconstitution.

2. Withdraw approximately 10 mL of the sterile diluent into a sterile syringe, inject it into the vial containing 0.5 mg 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 sterile diluent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanograms/mL epoprostenol. Only this concentrated solution is suitable for further dilution prior to use.

When 0.5 mg *FLOLAN* powder for i.v. infusion is reconstituted with 50 mL of sterile diluent, the final injection has a pH of approximately 12 and a sodium ion content of approximately 73 mg.

Dilution:

The concentrated solution is normally further diluted immediately prior to use. It may be diluted with sodium chloride 0.9% w/v (saline) solution, in a ratio of 2.3 volumes of saline to 1 volume of concentrated solution, e.g. 50 mL of concentrated solution further diluted with 117 mL of saline.

Other common i.v. fluids are unsatisfactory for the dilution of concentrated solution as the required pH is not attained. *FLOLAN* solutions are less stable at low pH.

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 chosen infusion solution using firm but not excessive pressure; the typical time taken for filtration of 50 mL of concentrated solution is 70 seconds. Mix well.

For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile physiological saline.

The final infusion solution (either as a concentrated solution or a further diluted solution) should be transferred into a suitable container or delivery system prior to administration. A 0.22 micron sterile syringe filter must be used during transfer.

The syringe filter unit must be used only during preparation and then discarded.

When reconstituted and diluted as directed above, *FLOLAN* infusion solutions have a pH of approximately 12.

Calculation of infusion rate:

The infusion rate may be calculated from the following formula:

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

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

Infusion rate formulae - examples

When used in renal dialysis *FLOLAN* may be administered as the concentrated solution (a) or in diluted form (b).

a. Using concentrated solution, i.e. 10,000 nanograms/mL *FLOLAN*:

Dosage (nanograms/ kg/min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
1	0.18	0.24	0.30	0.36	0.42	0.48	0.54	0.60
2	0.36	0.48	0.60	0.72	0.84	0.96	1.08	1.20
3	0.54	0.72	0.90	1.08	1.26	1.44	1.62	1.80
4	0.72	0.96	1.20	1.44	1.68	1.92	2.16	2.40
5	0.90	1.20	1.50	1.80	2.10	2.40	2.70	3.00
	Flow rates in **mL/h**							

b. Diluted: A commonly used dilution is:

15 mL concentrated solution + 35 mL physiological saline (0.9%).

Resultant concentration = 3,000 nanograms/mL *FLOLAN*:

Dosage (nanograms/ kg/min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
1	0.60	0.80	1.00	1.20	1.40	1.60	1.80	2.00
2	1.20	1.60	2.00	2.40	2.80	3.20	3.60	4.00
3	1.80	2.40	3.00	3.60	4.20	4.80	5.40	6.00
4	2.40	3.20	4.00	4.80	5.60	6.40	7.20	8.00
5	3.00	4.00	5.00	6.00	7.00	8.00	9.00	10.00
	Flow rates in **mL/h**							

Not all presentations are available in every country.

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