FLOLAN™
epoprost enol sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials containing sterile, freeze-dried epoprostenol sodium equivalent to 500 micrograms or 1.5 mg epoprostenol.

Epoprostenol was formerly known as prostacyclin.

PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

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*).

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.

Glycine buffer diluents 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

Hyperthyroidism

Very rare
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.

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$_1$alpha, although there is some enzymatic degradation to other products.

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

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

**Elimination**

The half-life for the spontaneous breakdown to 6-oxo-prostaglandin F$_1$alpha in man is expected to be no more than 6 minutes, and may be as short as 2 to 3 minutes, as estimated from *in vitro* rates of degradation of epoprostenol in human whole blood.

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

**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 40mg/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 1015mL/kg, and the whole body clearance to be 4.27mL/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

Glycine, sodium chloride, mannitol, sodium hydroxide BP.

Incompatibilities

*FLOLAN* must be reconstituted using only the sterile buffer 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*).

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Do not store *FLOLAN* vials above temperature 25°C. 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.

Store the sterile glycine buffer diluent at a temperature below 25°C. Do not freeze. Protect from light. Glycine buffer diluent contains no preservative, consequently a vial should be used once only and then discarded.

Reconstitution and dilution should be carried out immediately prior to use (*see Dosage and Administration, and Instructions for Use/Handling*).
Nature and Contents of Container

Freeze dried powder in glass vials with butyl rubber plugs and aluminium collars.

Sterile diluent in glass vials with synthetic butyl rubber plugs and aluminium collars with a flip-top cover.

Renal Dialysis

Vials containing sterile, freeze-dried epoprostenol equivalent to 500 micrograms epoprostenol, supplied with a 50 mL vial of sterile glycine buffer solution and a filter unit.

Instructions for Use/Handling

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, dilution and calculation of infusion rate

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

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

Renal Dialysis

The pack suitable for use in renal dialysis contains 500 micrograms freeze-dried epoprostenol plus 50 mL sterile diluent buffer.

Reconstitution:

1. Use only the sterile buffer solution provided for reconstitution.

2. Withdraw approximately 10 mL of the sterile buffer solution into a sterile syringe, inject it into the vial containing 500 micrograms 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 buffer solution 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 500 micrograms \textit{FLOLAN} powder for i.v. infusion is reconstituted with 50 mL of sterile buffer solution, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

\textbf{Dilution:}

The concentrated solution is normally further diluted before use. It may be diluted with physiological saline (0.9%), provided a ratio of 6 volumes of saline to 1 volume of concentrated solution is not exceeded; e.g. 50 mL of concentrated solution further diluted with a maximum of 300 mL saline.

Other common i.v. fluids are unsatisfactory for the dilution of concentrated solution as the required pH is not attained. \textit{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.

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, \textit{FLOLAN} infusion solutions have a pH of approximately 10 and will retain 90\% of their initial potency for approximately 12 hours at 25°C.

\textbf{Calculation of infusion rate:}

The infusion rate may be calculated from the following formula:

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

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

\textbf{Infusion rate formulae - examples}

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

\begin{itemize}
  \item [a.] Using concentrated solution, i.e. 10,000 nanograms/mL \textit{FLOLAN}: 
\end{itemize}
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:

10mL concentrated solution- 40mL physiological saline (0.9%).

Resultant concentration = 2000 nanograms/mL *FLOLAN*:

| Dosage (nanograms/kg/min) | Bodyweight (kg)
--- | ---
| 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100
--- | --- | --- | --- | --- | --- | --- | ---
1 | 0.90 | 1.20 | 1.50 | 1.80 | 2.10 | 2.40 | 2.70 | 3.00
2 | 1.80 | 2.40 | 3.00 | 3.60 | 4.20 | 4.80 | 5.40 | 6.00
3 | 2.70 | 3.60 | 4.50 | 5.40 | 6.30 | 7.20 | 8.10 | 9.00
4 | 3.60 | 4.80 | 6.00 | 7.20 | 8.40 | 9.60 | 10.80 | 12.00
5 | 4.50 | 6.00 | 7.50 | 9.00 | 10.50 | 12.00 | 13.50 | 15.00

Flow rates in mL/h

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

Not all presentations are available in every country.

**Version number:** GDS 22/ IPI 12SI

**Date of issue:** 11 July 2014

Manufactured by GlaxoSmithKline Manufacturing SPA, Parma, Italy.

*FLOLAN* is a trademark of the GlaxoSmithKline group of companies.