Flolan Infusion of Epoprostenol 500 mcg
Flolan Infusion of Epoprostenol 1500 mcg

1. NAME OF THE MEDICINAL PRODUCT

Flolan Infusion of Epoprostenol 500 mcg
Flolan Infusion of Epoprostenol 1500 mcg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Flolan Infusion of Epoprostenol 500 mcg
Each vial contains epoprostenol sodium equivalent to 0.5 mg epoprostenol.

One ml of reconstituted concentrate solution contains epoprostenol (as epoprostenol sodium) 10,000 nanogram (0.5 mg epoprostenol in 50 ml of solvent).

Flolan Infusion of Epoprostenol 1500 mcg
Each vial contains epoprostenol sodium equivalent to 1.5 mg epoprostenol.

One ml of reconstituted concentrate solution contains epoprostenol (as epoprostenol sodium) 30,000 nanogram (1.5 mg epoprostenol in 50 ml of solvent).

Excipients with known effect:
The amount of sodium present in the reconstituted concentrate solution equals 73 mg approximately.
The amount of sodium present in the powder for solution for infusion equals 3 mg approximately per vial.
The amount of sodium present in the solvent for parenteral use equals 70 mg approximately per vial.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for infusion.

Powder for solution for infusion:
- White to off-white solid

Solvent for parenteral use:
- Clear, colourless solution (pH 11.7 – 12.3)

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FLOLAN is indicated for the long term intravenous treatment of primary arterial pulmonary hypertension and arterial pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.

4.2 Posology and method of administration

Reconstitution

Each vial is for single use only; discard any unused diluent or unused reconstituted solution. Select a concentration for the solution of FLOLAN that is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed below *[see Administration]*.

Using aseptic technique, reconstitute FLOLAN only with pH 12 STERILE DILUENT for FLOLAN. Table 1 gives directions for preparing several different concentrations of FLOLAN. See Table 2 for storage and administration time limits for the reconstituted FLOLAN.

Table 1. Reconstitution and Dilution Instructions for FLOLAN Using pH 12 STERILE DILUENT for FLOLAN.

To make 100 mL of solution with final concentration of:	**Directions:**
3,000 ng/mL	Dissolve contents of **one 0.5-mg vial** with 5 mL of sterile diluent. Withdraw 3 mL and add to sufficient sterile diluent to make a total of 100 mL.
5,000 ng/mL	Dissolve contents of **one 0.5-mg vial** with 5 mL of sterile diluent. Withdraw entire vial contents and add sufficient sterile diluent to make a total of 100 mL.
10,000 ng/mL	Dissolve contents of **two 0.5-mg vials** each with 5 mL of sterile diluent. Withdraw entire vial contents and add sufficient sterile diluent to make a total of 100 mL.
15,000 ng/mL[a]	Dissolve contents of **one 1.5-mg vial** with 5 mL of sterile diluent. Withdraw entire vial contents and add sufficient sterile diluent to make a total of 100 mL.

[a] Higher concentrations may be prepared for patients who receive FLOLAN long-term.

Table 2. Storage and Administration Limits for Reconstituted FLOLAN

	When Using pH 12 STERILE DILUENT for FLOLAN
Stability	Freshly prepared reconstituted solutions or reconstituted solutions that have been stored at 2°C to 8°C for no longer than 8 days can be administered up to: • 72 hours at up to 25°C. • 48 hours at up to 30°C. • 24 hours at up to 35°C. • 12 hours at up to 40°C.
• Reconstituted solutions can be used immediately. Refrigerate at 2°C to 8°C if not used immediately. • Protect from light. • Do not freeze reconstituted solutions.	

Dosage

Initiate intravenous infusions of FLOLAN at 2 ng/kg/min. Alter the infusion by 1- to 2 -ng/kg/min increments at intervals sufficient to allow assessment of clinical response. These intervals should be at least 15 minutes.

During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output may occur. In such cases, consider dose reduction, but such an increase does not imply that chronic treatment is contraindicated.

Base changes in the chronic infusion rate on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse vasodilatory reactions. In general, expect progressive increases in dose.

If dose-related adverse reactions occur, make dose decreases gradually in 2 -ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve *[see section 4.8 Undesirable effects]*. Avoid abrupt withdrawal of FLOLAN or sudden large reductions in infusion rates *[see section 4.4 Special warnings and precautions for use]*.

Following establishment of a new chronic infusion rate, measure standing and supine blood pressure for several hours.
Taper doses of FLOLAN after initiation of cardiopulmonary bypass in patients receiving lung transplants.

Administration

Initiate FLOLAN in a setting with adequate personnel and equipment for physiologic monitoring and emergency care.

Inspect parenteral drug products for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, do not use.

Administer continuous chronic infusion of FLOLAN through a central venous catheter. Temporary peripheral intravenous infusion may be used until central access is established. Do not administer bolus injections of FLOLAN.

The ambulatory infusion pump used to administer FLOLAN should: (1) be small and lightweight, (2) be able to adjust infusion rates in 2-ng/kg/min increments, (3) have occlusion, end-of-infusion, and low-battery alarms, (4) be accurate to ±6% of the programmed rate, and (5) be positive-pressure-driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver FLOLAN. The reservoir should be made of polyvinyl chloride, polypropylene, or glass. Use a 60-inch microbore non-di-(2-ethylhexyl)phthalate (DEHP) extension set with proximal antisyphon valve, low priming volume (0.9 mL), and in-line 0.22-micron filter.

Preparation and administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG) may become damaged when used with FLOLAN prepared with pH 12 STERILE DILUENT for FLOLAN and therefore must not be used.

Consult the manufacturer of the sets to confirm that they are considered compatible with highly alkaline solutions, such as FLOLAN prepared with pH 12 STERILE DILUENT for FLOLAN.

To avoid interruptions in drug delivery, the patient should have access to a backup infusion pump and intravenous infusion sets.
Do not administer or dilute reconstituted solutions of FLOLAN with other parenteral solutions or medications. Consider a multi-lumen catheter if other intravenous therapies are routinely administered.

Select a concentration for the solution of FLOLAN that is compatible with the infusion pump being used with respect to minimum and maximum flow rates, reservoir capacity, and the infusion pump criteria listed above. When administered chronically, prepare FLOLAN in a drug delivery reservoir appropriate for the infusion pump with a total reservoir volume of at least 100 mL, using 2 vials of pH 12 STERILE DILUENT for FLOLAN.

Generally, 3,000 ng/mL and 10,000 ng/mL are satisfactory concentrations to deliver between 2 to 16 ng/kg/min in adults. Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of FLOLAN.

Infusion rates may be calculated using the following formula:

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

Example calculations for infusion rates are as follows:

Example 1: for a 60-kg person at the recommended initial dose of 2 ng/kg/min using a 3,000-ng/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate} \text{ (mL/h)} = \frac{\textbf{[2} \text{ (ng/kg/min)} \textbf{ x 60} \text{ (kg)} \textbf{ x 60 (}\text{min/h)}\textbf{]}}{\textbf{3,000} \text{ (ng/mL)}} = \textbf{2.4} \text{ (mL/h)}$$

Example 2: for a 70-kg person at a dose of 16 ng/kg/min using a 15,000-ng/mL concentration, the infusion rate would be as follows:

$$\textbf{Infusion Rate} \text{ (mL/h)} = \frac{\textbf{[16} \text{ (ng/kg/min)} \textbf{ x 70} \text{ (kg)} \textbf{ x 60 (}\text{min/h)}\textbf{]}}{\textbf{15,000} \text{ (ng/mL)}} = \textbf{4.48} \text{ (mL/h)}$$

4.3 Contraindications

Flolan is contraindicated in patients:

- with known hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.
- with congestive heart failure arising from severe left ventricular dysfunction.
- Flolan must not be used chronically in patients who develop pulmonary oedema during dose-ranging.

4.4 Special warnings and precautions for use

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 section 4.5).

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).

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.

Extreme caution is advised in patients with coronary artery disease.

Elevated serum glucose levels have been reported (see section 4.8).

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

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

The amount of sodium present in the reconstituted concentrate solution equals 73 mg approximately, equivalent to approximately 4 % of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

The amount of sodium present in the powder for solution for infusion equals 3 mg approximately per vial, equivalent to approximately 0.2 % of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

The amount of sodium present in the solvent for parenteral use equals 70 mg approximately per vial, equivalent to approximately 4 % of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

Some patients with pulmonary arterial hypertension have developed pulmonary oedema during dose-ranging, which may be associated with pulmonary veno-occlusive disease. Flolan must not be used chronically in patients who develop pulmonary oedema during dose initiation (see section 4.3).

Abrupt withdrawal or interruption of infusion must be avoided, except in life-threatening situations. An abrupt interruption of therapy can induce a rebound of pulmonary arterial hypertension resulting in dizziness, asthenia, increased dyspnoea, and may lead to death (see section 4.2).

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. Even brief interruptions in the delivery of Flolan may result in rapid symptomatic deterioration. The decision to administer Flolan for pulmonary arterial hypertension 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 i.v. catheter and infusion pump should be carefully considered.

4.5 Interaction with other medicinal products and other forms of interaction

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.

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.

4.6 Fertility, pregnancy, and lactation

Pregnancy
There is a limited amount of data from the use of epoprostenol in pregnant women.
Animal studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).
Given the absence of alternative medicines, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy.

Breast-feeding
It is unknown if epoprostenol or its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Breast-feeding should be discontinued during treatment with Flolan.

Fertility
There are no data on the effects of epoprostenol on fertility in humans. Reproductive studies in animals have shown no effects on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Pulmonary arterial hypertension and its therapeutic management may affect the ability to drive and operate machinery.

4.8 Undesirable effects

Adverse events 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%) and not known (cannot be estimated from the available data).

Infections and Infestations	
Common	Sepsis, septicaemia (mostly related to delivery system for Flolan)[1]
Blood and Lymphatic System Disorders	
Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
Unknown	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[2], bradycardia[3]
Not known	High output cardiac failure
Vascular Disorders	
Very common	Facial flushing (seen even in the anaesthetised patient)
Common	Hypotension
Very rare	Pallor
Not known	Ascites
Respiratory, thoracic and mediastinal disorders	
Unknown	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	Erythema over the infusion site*, occlusion of the long i.v. catheter*, lassitude, chest tightness
Investigations	
Unknown	Blood glucose increased
* Associated with the delivery system for Flolan	
[1] Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.	
[2] Tachycardia has been reported as a response to Flolan at doses of 5 nanograms/kg/min and below.	
[3] Bradycardia, sometimes accompanied by 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.	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

Additionally, you should also report to GSK Israel (il.safety@gsk.com).

4.9 Overdose

The main feature of overdose is likely to be hypotension.

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

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic Agents; Platelet aggregation inhibitors excl. heparin, ATC code: B01AC09

Mechanism of action
Epoprostenol Sodium, 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 depends.

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

Intravenous epoprostenol infusions of up to 15 minutes have been found to produce dose-related increases in cardiac index (CI) and stroke volume (SV), and dose-related decreases in pulmonary vascular resistance (PVR), total pulmonary resistance (TPR) and mean systemic arterial pressure (SAPm). The effects of epoprostenol on mean pulmonary artery pressure (PAPm) in patients with PPH were variable and minor.

Clinical efficacy and safety

Chronic continuous infusions of epoprostenol in patients with idiopathic or heritable PAH were studied in 2 prospective, open, randomised trials of 8 and 12 weeks' duration (N=25 and N=81, respectively) comparing epoprostenol plus conventional therapy to conventional therapy alone. Conventional 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 the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are described. The combined baseline 6-minute walk test median values for the conventional therapy group and epoprostenol plus conventional therapy group was 266 meters and 301 meters, respectively.

Improvements from baseline in cardiac index (0.33 vs. -0.12 L/min/m^2), stroke volume (6.01 vs. -1.32 mL/beat), arterial oxygen saturation (1.62 vs. -0.85%), mean pulmonary artery pressure (-5.39 vs. 1.45 mm Hg), mean right atrial pressure (-2.26 vs. 0.59 mm Hg), total pulmonary resistance (-4.52 vs. 1.41 Wood U), pulmonary vascular resistance (-3.60 vs. 1.27 Wood U), and systemic vascular resistance (-4.31 vs. 0.18 Wood U) were statistically different between patients who received epoprostenol chronically and those who did not. Mean systemic arterial pressure was not significantly different between the two groups (-4.33 vs. -3.05 mm Hg). These haemodynamic improvements appeared to persist when epoprostenol was administered for at least 36 months in an open, nonrandomized study.

Statistically significant improvement was observed in exercise capacity (p=0.001), as measured by the 6MWT in patients receiving continuous intravenous epoprostenol plus conventional therapy (N=52) for 8 or 12 weeks compared to those receiving conventional therapy alone (N=54) (combined week 8 and 12 change from baseline – median: 49 vs. -4 meters; mean: 55 vs. -4 meters). Improvements were apparent as early as the first week of therapy. At the end of the treatment period in the 12 weeks study, survival was improved in NYHA functional Class III and Class IV patients. Eight of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died (p=0.003).

Chronic continuous infusions of epoprostenol in patients with PAH/SSD were studied in a prospective, open, randomised trial of 12 weeks' duration comparing epoprostenol plus conventional therapy (N = 56) to conventional therapy alone (N = 55). Except for 5 NYHA functional Class II patients, all patients were either functional Class III or Class IV. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. The primary efficacy endpoint for the study was improvement in the 6MWT. The median baseline value for the conventional therapy group and epoprostenol plus conventional therapy group was 240 meters and 270 meters, respectively. A statistically significant increase in CI, and statistically significant decreases in PAPm, RAPm, PVR, and SAPm after 12 weeks of treatment were observed in patients who received epoprostenol chronically compared to those who did not.

Over 12 weeks, a statistical difference ($p<0.001$) in the change from baseline for the 6MWT was observed in the group receiving epoprostenol and conventional therapy as compared to the group receiving conventional therapy alone (median: 63.5 vs. -36.0 meters; mean: 42.9 vs. -40.7 meters).
Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnoea, as measured by the Borg Dyspnea Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol and 13/48 (27%) with conventional therapy alone worsened.

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

5.2 Pharmacokinetic properties

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.

Intravenously administered epoprostenol is rapidly distributed from blood to tissue.
At normal physiological pH and temperature, epoprostenol 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.

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.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. No long-term animal studies have been conducted to determine the carcinogenic potential of epoprostenol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for infusion:
Mannitol
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)

Solvent for parenteral use:
Glycine
Sodium Chloride
Sodium Hydroxide (for pH adjustment)
Water for Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Preparation and administration materials containing PET or PETG may become damaged when used with epoprostenol solution prepared with solvent (pH 11.7-12.3) and therefore must not be used (see section 6.6).

6.3 Shelf life

Unopened vials

The expiry date of the product is indicated on the label and packaging materials.

Stability during administration

Freshly prepared reconstituted solutions or reconstituted solutions that have been stored at 2°C to 8°C for no longer than 8 days can be administered up to::

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

Discard any unused solution after this time.

Reconstituted solutions can be used immediately. Refrigerate at 2°C to 8°C if not used immediately. Protect from light. Do not freeze reconstituted solutions.

6.4 Special precautions for storage

Powder for solution for infusion:
Do not store vials above 25°C. Protect from light. Keep dry. Do not freeze. Store in the original package.

Solvent for parenteral use:
Do not store vials above 25°C. Do not freeze. Protect from light. Keep Dry. Store in the original package.
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Powder for solution for infusion:
Clear (type 1) glass vials with synthetic butyl rubber stoppers and an aluminium collar with a snap-off top.

Solvent for parenteral use:
Clear plastic vials with synthetic butyl rubber stoppers and an external aluminium collar with a purple plastic flip-top cover.

Pack sizes:

Flolan Infusion of Epoprostenol 500 mcg
There are two presentations available in 0.5 mg for use in the treatment of pulmonary arterial hypertension, as follows:
- One 0.5 mg powder vial and one solvent vial and a filter unit.
- One 0.5 mg powder vial and two solvent vials and a filter unit.

Flolan Infusion of Epoprostenol 1500 mcg
There is one presentation available in 1.5 mg for use in the treatment of pulmonary arterial hypertension, as follows:
- One 1.5 mg powder vial and two solvent vials and a filter unit.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The stability of solutions of Flolan is pH dependent. Only the solvent 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 using aseptic technique.

Epoprostenol solution prepared with solvent (pH 11.7-12.3), must not be used with any preparation or administration materials containing PET or PETG (see section 6.2). Based on available data from inhouse testing and published literature, preparation and administration materials likely to be compatible include:

- Modified Acrylic
- Acrylonitrile butadiene styrene (ABS)
- Cyclic olefin polymer
- Polyamide
- Polyethersulfone
- Polyethylene
- Polyisoprene
- Polyolefin
- Polypropylene
- Polytetrafluoroethylene (PTFE)
- Polyurethane
- Polyvinyl chloride (PVC) (plasticised with bis(2-ethylhexyl) phthalate [DEHP])
- Polyvinylidene fluoride (PVDF)
- Silicone

Suitable ambulatory pumps to be used include:

- CADD-Legacy 1
- CADD-Legacy PLUS
- CADD-Solis VIP (variable infusion profile)
  Manufactured by Smiths Medical.

Pump accessories found to be compatible include:

- CADD disposable Medication Cassette Reservoir 50 mL; 100 mL from Smiths Medical.
- CADD extension set with in-line 0.2 micron filter (CADD extension set with male luer, 0.2- micron air-eliminating filter, clamp, and integral anti-siphon valve with male luer) from Smiths Medical. The extension set and the in-line filter must be changed at least every 48 hours.

7. MANUFACTURER

GlaxoSmithKline Manufacturing S.p.A., Parma, Italy.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBER

Flolan infusion of epoprostenol 500 mcg: 126 72 30642
Flolan infusion of epoprostenol 1500 mcg: 112 41 29467

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*Flo DR v*9