SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Flolan 1.5 mg powder and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Epoprostenol 1.5 mg powder for solution for infusion:
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 or off-white freeze dried powder

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Flolan is indicated for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III-IV symptoms to improve exercise capacity (see section 5.1).

4.2 Posology and method of administration

Posology

Epoprostenol is only indicated for continuous infusion by intravenous route.

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

Short-term (acute) dose ranging:

This procedure should be conducted in a hospital with adequate resuscitation equipment.

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 nanograms/kg/min and increased by increments of 2 nanograms/kg/min every 15 min or longer until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited.
If the initial infusion rate of 2 nanograms/kg/min is not tolerated, a lower dose which is tolerated by the patient should be identified.

Long-term continuous infusion:

Long-term continuous infusion of Flolan should be administered through a central venous catheter. Temporary peripheral i.v. infusions may be used until central access is established. Long-term infusions should be initiated at 4 nanograms/kg/min less than the maximum tolerated infusion rate determined during short-term dose-ranging. If the maximum tolerated infusion rate is 5 nanograms/kg/min or less, then the long-term infusion should be started at 1 nanograms/kg/min.

Dosage adjustments:

Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of pulmonary arterial hypertension or the occurrence of adverse reaction 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 pulmonary arterial hypertension persist, or recur after improving. The infusion rate should be increased by 1 to 2 nanograms/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be of at least 15 min. 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.

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 reactions may occasionally resolve without dosage adjustment. Dosage decreases should be made gradually in 2 nanograms/kg/min decrements every 15 min or longer until the dose-limiting effects resolve. Abrupt withdrawal of Flolan or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effect (see section 4.4). Except in life-threatening situations (e.g. unconsciousness, collapse, etc) infusion rates of Flolan should be adjusted only under the direction of a physician.

Elderly
There is no specific information on the use of Flolan in patients over 65 years for pulmonary arterial hypertension. 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 medicine therapy.

Paediatric population
The safety and efficacy of epoprostenol in children younger than 18 years have not yet been established.

Method of administration

Precautions to be taken before handling or administering the medicinal product

Freshly prepared solutions for infusion (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for up to 8 days at 2 °C to 8 °C prior to administration. Following this preparation or storage, the solution for infusion should be used within 48 hours at up to 25 °C, or 36 hours at up to 30 ºC, or 24 hours at up to 35 ºC, or 12 hours at up to 40 ºC (see section 6.3).

Epoprostenol solution prepared with solvent (pH 11.7-12.3), must not be used with any preparation or administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG; see section 6.2 and 6.6).

The reconstituted solution should be examined prior to administration. Its use is forbidden in the presence of a discoloration or particles.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Epoprostenol must not be administered as a bolus injection.

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 as there may be potentiation of effect.

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

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 platelets aggregation are used concomitantly, there is the potential for Flolan to increase the risk of bleeding.

Patients on digoxin have shown elevations of digoxin concentrations after initiation of therapy with Flolan. This may be clinically relevant in patients prone to digoxin toxicity. Monitoring of digoxin levels is therefore advisable until digoxin levels are clinically stable in patients receiving treatment with Flolan and digoxin.

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 ≥1/1 000 and <1/100 (≥0.1% and <1%); rare ≥1/10 000 and <1/1 000 (≥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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

Powder for solution for infusion: 3 years

Solvent for parenteral use: 36 months

Stability during administration

For solutions ≤ 150 000 ng/mL:

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

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

Discard any unused solution after this time.

For solutions >150 000 ng/mL and ≤300 000 ng/mL:

Reconstituted solutions that have been stored at 2 to 8 ℃ for up to 7 days can be administered for up to 24 hours at 25 ℃.
Freshly prepared reconstituted solutions, or solutions that have been stored at 2 to 8 ℃ for no longer than 5 days can be administered for up to:

- 48 hours at up to 25 °C or
- 24 hours at up to 35 °C

Discard any unused solution after this time.

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. 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.

Vial adaptor:
A polycarbonate vial adaptor with PTFE filter and silicone stem

Pack sizes:
There are three presentations available in 1.5 mg for use in the treatment of pulmonary arterial hypertension, as follows:
- One 1.5 mg powder vial and one solvent vial, a vial adaptor and a filter unit.
- One 1.5 mg powder vial and two solvent vials, two vial adaptors and a filter unit.
- One 1.5 mg powder vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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.

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.

There are three 1.5 mg packs available for use in the treatment of pulmonary arterial hypertension, as follows:

- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan, supplied with one 50 mL vial of solvent, a vial adaptor and a filter unit.
- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan, supplied with two 50 mL vials of solvent, two vial adaptors and a filter unit.
- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan supplied alone.

There are also three 0.5 mg packs available for use in the treatment of pulmonary arterial hypertension.

Initially a pack containing solvent for parenteral use must be used. During chronic Flolan therapy higher concentrated solutions may be required. The final concentration of the solution may be increased by the addition of further 1.5 mg vials of freeze-dried Flolan.

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

Reconstitution:

1. Use only the sterile solvent solution provided for reconstitution.
2. Withdraw approximately 10 mL of the sterile solvent solution into a sterile syringe, through a vial adaptor*
3. Remove syringe from vial adaptor. Attach needle to syringe, inject the 10 mL of sterile solvent into the vial containing the freeze-dried epoprostenol and shake gently until the powder has dissolved.
4. Draw up the resulting epoprostenol solution into the syringe, remove the needle, re-inject it into the remaining volume of the sterile solvent solution through the vial adaptor* and mix thoroughly.

* Alternatively, a needle may be used in place of a vial adaptor.

This solution is now referred to as the concentrated solution.

- Where a pack containing 1.5 mg epoprostenol is reconstituted with 50 mL sterile solvent the resultant concentration is 30 000 nanograms/mL.

Dilution:

Flolan may be used either as a concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only concentrated solutions are suitable for further dilution with the sterile solvent prior to use.

Only the solvent provided may be used for the further dilution of reconstituted Flolan, using a new vial adaptor for each additional sterile solvent vial required. Sodium chloride 0.9% w/v solution must not be used when Flolan is to be used for the treatment of pulmonary arterial hypertension as the required pH is not maintained. Flolan solutions are less stable at low pH. Flolan must not be administered with other parenteral solutions or medications when used for pulmonary arterial hypertension.
The final solution to be administered to the patient must be filtered using a 0.22 or 0.20 micron filter. Use of an in-line filter as part of the infusion set during administration is preferable. Alternatively, where in-line filtration is not possible, the final solution (either a concentrated or further diluted solution) must be filtered with the provided sterile 0.22 micron filter prior to storage in the medication cassette using firm but not excessive pressure; the typical time taken for filtration of 50 mL of solution is 70 seconds.

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

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

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

15 000 nanograms/mL - 1.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.
30 000 nanograms/mL - Two vials containing 1.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.

Calculation of infusion rate:

The infusion rate may be calculated from the following formula:

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

Infusion rate (mL/h) = Infusion rate (mL/min) x 60

Examples for some concentrations commonly used in pulmonary arterial hypertension are shown below.

Infusion rates for a concentration of 15 000 nanograms/mL

Example For Dosing Using a Concentration of 15 000 nanograms/mL								
Dosage (nanograms/kg/min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
4	0.5	0.6	0.8	1.0	1.1	1.3	1.4	1.6
6	0.7	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/h**							

Infusion rates for a concentration of 30 000 nanograms/mL

Example For Dosing Using a Concentration of 30 000 nanograms/mL								
Dosage (nanograms/kg/ min)	Bodyweight (kg)							
	30	40	50	60	70	80	90	100
6	0.4	0.5	0.6	0.7	0.8	1.0	1.1	1.2
8	0.5	0.6	0.8	1.0	1.1	1.3	1.4	1.6
10	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0
12	0.7	1.0	1.2	1.4	1.7	1.9	2.2	2.4
14	0.8	1.1	1.4	1.7	2.0	2.2	2.5	2.8
16	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2
18	1.1	1.4	1.8	2.2	2.5	2.9	3.2	3.6
20	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0
	Flow rates in **mL/h**							

Higher infusion rates, and therefore, more concentrated solutions may be necessary with long-term administration of Flolan.

7 MARKETING AUTHORISATION HOLDER

Glaxo Wellcome UK Ltd
Trading as GlaxoSmithKline UK
GSK Medicines Research Centre
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8 MARKETING AUTHORISATION NUMBER(S)

Flolan 1.5mg Injection PL10949/0312

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7th March 2001

10 DATE OF REVISION OF THE TEXT

16/11/2023