

## **Annex III**

### **Summary of product characteristics, labelling and package leaflet**

Note:

This SmPC, labelling and package leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SmPC, labelling and package leaflet may not necessarily represent the current text.

**SUMMARY OF PRODUCT CHARACTERISTICS,  
LABELLING AND PACKAGE LEAFLET**

## **SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Flolan 0.5 mg Powder and Solvent for Solution for Infusion  
Flolan 1.5 mg Powder and Solvent for Solution for Infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Epoprostenol 0.5mg Powder for Solution for Infusion:  
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.

Epoprostenol 1.5mg 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 ) 30 000 nanogram.

The amount of sodium present in the reconstituted concentrate solution equals 55.9 mg approximately.  
The amount of sodium present in the powder for solution for infusion equals 2.7 mg approximately per vial.

The amount of sodium present in the solvent for parenteral use equals 53.2 mg approximately per vial.

For a full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion:  
- White or off-white freeze dried powder

Solvent for parenteral use:  
- Clear, colourless solution (pH 10.3 – 10.8)

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Flolan is indicated for:

Pulmonary Arterial Hypertension

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).

Renal Dialysis

Flolan is indicated for use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated (see section 5.1).

### 4.2 Posology and method of administration

Posology

Epoprostenol is only indicated for continuous infusion by intravenous route.

#### Pulmonary Arterial Hypertension

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

#### Dosage adjustments:

Changes in the long-term infusion rate should be based on persistence, recurrence or worsening of the patient's symptoms of 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.

#### 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 mins

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.

#### *Elderly*

There is no specific information on the use of Flolan in patients over 65 years for renal dialysis or pulmonary arterial 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 arterial hypertension) 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

##### *Preparation of Flolan intravenous injectable solution:*

Reconstituted solutions, prepared in real time, must not be administered over more than 12 hours when they are used at room temperature (between 15°C and 25°C). They should be kept under 25°C and protected from light.

It is possible to refrigerate Flolan reconstituted solutions, before they are used at room temperature, ranging between 2°C and 8°C and without exceeding 40 hour storage. In this case, the solutions should not be used over more than 8 hours when administered at room temperature.

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

For further 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). Pulmonary Arterial Hypertension 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 edema 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, increase 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.

##### **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. Flolan 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.

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

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

#### **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.

##### **Breastfeeding**

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.

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

#### **4.8 Undesirable effects**

Adverse events are listed below by system organ class and frequency. Frequencies are defined as follows: very common  $\geq 1/10$  ( $\geq 10\%$ ); common  $\geq 1/100$  and  $< 1/10$  ( $\geq 1\%$  and  $< 10\%$ ); uncommon  $\geq 1/1000$  and  $< 1/100$  ( $\geq 0.1\%$  and  $< 1\%$ ); rare  $\geq 1/10,000$  and  $< 1/1000$  ( $\geq 0.01\%$  and  $< 0.1\%$ ); very rare  $< 1/10,000$  ( $< 0.01\%$ ) and not known (cannot be estimated from the available data).

<b>Infections and Infestations</b>	
Common	Sepsis, septicaemia (mostly related to delivery system for Flolan) <sup>1</sup>
<b>Blood and Lymphatic System Disorders</b>	
Common	Decreased platelet count, bleeding at various sites (e.g. pulmonary, gastrointestinal, epistaxis, intracranial, post-procedural, retroperitoneal)
<b>Endocrine Disorders</b>	
Very rare	Hyperthyroidism
<b>Psychiatric Disorders</b>	
Common	Anxiety, nervousness
Very rare	Agitation
<b>Nervous System Disorders</b>	
Very common	Headache
<b>Cardiac Disorders</b>	
Common	Tachycardia <sup>2</sup> , bradycardia <sup>3</sup> ,
<b>Vascular Disorders</b>	
Very common	Facial flushing (seen even in the anaesthetised patient)
Common	Hypotension
Very rare	Pallor
<b>Respiratory, thoracic and mediastinal disorders</b>	
Unknown	Pulmonary oedema
<b>Gastrointestinal Disorders</b>	
Very common	Nausea, vomiting, diarrhoea
Common	Abdominal colic, sometimes reported as abdominal discomfort
Uncommon	Dry mouth
<b>Skin and Subcutaneous Tissue Disorders</b>	
Common	Rash
Uncommon	Sweating
<b>Musculoskeletal and Connective Tissue Disorders</b>	
Very common	Jaw pain
Common	Arthralgia
<b>General Disorders and Administration Site Conditions</b>	
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
<b>Investigations</b>	
Unknown	Blood glucose increased
* Associated with the delivery system for Flolan	
<sup>1</sup> Catheter-related infections caused by organisms not always considered pathogenic (including micrococcus) have been reported.	
<sup>2</sup> Tachycardia has been reported as a response to Flolan at doses of 5 nanograms/kg/min and below.	

<sup>3</sup> 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.

## 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**

Infusion 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.

#### **Pulmonary Arterial Hypertension**

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.

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<sup>2</sup>), 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.

### **Renal Dialysis**

The effects of epoprostenol 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 epoprostenol to return to baseline within 10 minutes of termination of 60 minutes infusion at 1 to 16 nanograms/kg/min.

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

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

Six heparin-controlled studies and five emergency studies explored the place of epoprostenol in the general management of renal dialysis, using different techniques. Primary measurements of efficacy included intradialytic removal of BUN and creatinine, intradialytic removal of fluid (ultrafiltration), and clotting within the extracorporeal circuit.

Major clotting (dialysis permanently suspended, or requiring changing of artificial kidney) occurred in approximately 9% (n=56) of all epoprostenol dialyses and in <1% (n=1) of heparin dialyses in major controlled studies and emergency studies. Most epoprostenol dialyses (67%) that required replacement of artificial kidney were completed subsequently with epoprostenol without clotting. However, 9 of 27 epoprostenol dialyses were unsuccessful following multiple attempts.

Independent of technical difficulties which occurred rarely with either treatment, major dialysis-limiting clotting did not occur in 93% of all epoprostenol dialyses and 99% of all heparin dialyses.

Minor clotting (sufficient to require intervention, but not permanently suspending dialysis or requiring changing of the artificial kidney) was reported more frequently during epoprostenol than during heparin dialyses. None of the dialyses using heparin and 5% (n=32) of dialyses using epoprostenol had minor clotting.

Visible clotting (not necessitating intervention) was reported in another 31% of epoprostenol dialyses and 5% of heparin dialyses.

To establish that renal dialysis patients at increased risk of haemorrhage bleed less frequently with epoprostenol than heparin, 2 major prospectively controlled studies were conducted. Each patient was randomly assigned to a sequence of heparin or epoprostenol dialyses and received up to 6 dialyses per entry in one study and up to 3 dialyses per entry in another study.

Bleeding risk was defined as:

- Very high risk – presence of active bleeding at the time of dialysis initiation
- High risk – having had within 3 days prior to dialysis an active bleed that stopped at the pre-dialysis phase; or having incurred surgical or traumatic wounds within 3 days prior to dialysis

Twelve patients at very high risk of haemorrhage received 35 epoprostenol dialyses and 11 patients received 28 heparin dialyses in major controlled studies. Sixteen patients received 24 epoprostenol dialyses in emergency studies.

In major controlled studies, when all dialyses were combined for each treatment (heparin or epoprostenol), more heparin patients bled during the day prior to dialysis (N=13/17 vs. 8/23), dialysis day (N=25/28 vs. 16/35) and the day following dialysis (N=16/24 vs. 5/24) than epoprostenol patients during the same time periods.

Those patients who continued to bleed were evaluated for changes in bleeding severity. Severity of bleeding in those patients was improved more frequently with epoprostenol the day prior to dialysis and on dialysis day (predialysis: N=4/8; dialysis: N=6/16) than with heparin (predialysis: N=4/13; dialysis: N=4/25). However, the reverse was observed for postdialysis days with epoprostenol (N=1/5) compared to heparin (N=8/16). Bleeding severity worsened during only 1 dialysis day with epoprostenol (N=1/16) whereas severity worsened during 5 dialysis days (N=5/25) and 2 predialysis days (N=2/13) with heparin.

Patients who did not have clear evidence of bleeding just prior to their first study dialysis, but who bled within 3 days prior were classified as high risk of haemorrhage. Nineteen patients received 51 heparin dialyses and 19 received 44 epoprostenol dialyses in major controlled studies.

When all dialyses were combined, slightly more epoprostenol patients appeared to bleed during the predialysis (N=12/25 vs. 8/32), dialysis (23/44 vs. 14/51) and postdialysis (8/34 vs. 5/44) days compared to heparin patients during the same periods.

## **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<sub>1</sub> 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<sub>1</sub> 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 4.2.

## 6.3 Shelf life

Powder and Solvent for solution for infusion: 3 years.

*In use shelf life reconstituted/solvent solution for infusion:*

Reconstituted solutions must not be administered over more than 12 hours when they are used at room temperature (between 15°C and 25°C). They should be kept under 25°C and protected from light. Where the infusion pump allows the use of a cold pouch, the solution may be used over a 24 hour period, provided the cold pouch is changed as necessary throughout the day.

It is possible to refrigerate Flolan reconstituted solutions, before they are used at room temperature, ranging between 2°C and 8°C and without exceeding 40 hour storage. In this case, the solutions should not be used over more than 8 hours when administered at room temperature.

## 6.4 Special precautions for storage

*Powder for solution for infusion:*

Store vials below 25°C. Protect from light. Keep dry. Do not freeze. Store in the original package.

*Solvent for parenteral use:*

Store the solvent below 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.

Reconstitution and dilution should be carried out immediately prior to use (see section 4.2, section 6.3 and Section 6.6).

Freshly prepared epoprostenol solutions for the treatment of pulmonary arterial hypertension should be used within 12 hours at 25°C, or stored for up to 40 hours at between 2 to 8°C and then used within 8 hours at

25°C. Where the infusion pump allows the use of a cold pouch, epoprostenol solution may be used over a 24 hour period, provided that the cold pouch is changed as necessary throughout the day.

## 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 (type 1) glass vials with synthetic butyl rubber stoppers and an external aluminium collar with a plastic flip-top cover.

Pack sizes:

Pulmonary Arterial Hypertension

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

- One 0.5 mg powder vial and one or two solvent vials and a filter unit.
- One 1.5 mg powder vial and one or two solvent vials and a filter unit.
- One 0.5 mg powder vial.

- One 1.5 mg powder vial.

#### Renal Dialysis

Only the 0.5 mg pack is suitable for use in renal dialysis.

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, 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 0.5 mg freeze-dried Flolan plus 50 mL solvent.

#### **Reconstitution:**

Use only the solvent provided for reconstitution.

Withdraw approximately 10 mL of the solvent into a sterile syringe, inject it into the vial containing 0.5 mg freeze-dried Flolan powder and shake gently until the powder has dissolved.

Draw up the resulting Flolan solution into the syringe, re-inject it into the remaining volume of the solvent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanograms/mL Flolan. 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 solvent, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

#### **Dilution:**

The concentrated solution is normally further diluted before use. It may be diluted with sodium chloride 0.9% w/v solution, provided a ratio of 6 volumes of sodium chloride 0.9% w/v solution to 1 volume of concentrated solution is not exceeded e.g. 50 mL of concentrated solution further diluted with a maximum of 300 mL sodium chloride 0.9% w/v solution.

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.

The filter unit must be used once only and then discarded.

When reconstituted and diluted as directed above, Flolan infusion solutions have a pH of approximately 10 and will retain 90% of their initial potency for approximately 12 hours at 25°C.

**Calculation of infusion rate:**

The infusion rate may be calculated from the following formula:

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

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

**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 <b>mL/h</b>								

b. *Diluted*: A commonly used dilution is:

10 mL concentrated solution + 40 mL sodium chloride 0.9% w/v solution.

Resultant concentration = 2,000 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 <b>mL/h</b>								

For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile sodium chloride 0.9% w/v solution.

**Pulmonary Arterial Hypertension**

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

- One vial containing sterile, freeze-dried Flolan equivalent to 0.5 mg Flolan, supplied with one or two 50 mL vials of solvent and a filter unit.

- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan, supplied with one or two 50 mL vials of solvent and a filter unit.
- One vial containing sterile, freeze-dried Flolan equivalent to 0.5 mg Flolan supplied alone.
- One vial containing sterile, freeze-dried Flolan equivalent to 1.5 mg Flolan supplied alone.

Initially a pack containing solvent for parenteral use must be used. During chronic Flolan therapy the final concentration of solution may be increased by the addition of a further 0.5 mg or 1.5 mg vial of freeze-dried Flolan.

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

**Reconstitution:**

This should be carried out according to the instructions given for renal dialysis. Where a pack containing 1.5 mg Flolan is reconstituted with 50 mL solvent the resultant concentration is 30,000 nanograms/mL.

**Dilution:**

Flolan may be used either as concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only the solvent provided may be used for the further dilution of reconstituted Flolan. Sodium chloride 0.9% w/v solution must not be used when Flolan is to be used for the treatment of pulmonary arterial hypertension. Flolan must not be administered with other parenteral solutions or medications when used for pulmonary arterial hypertension.

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

The filter unit must be used once only and then discarded.

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

5,000 nanograms/mL - One vial containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.

10,000 nanograms/mL - Two vials containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.

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

### Calculation of infusion rate:

The infusion rate may be calculated from the formula given above for renal dialysis. Examples for some concentrations commonly used in pulmonary arterial hypertension are shown below.

Infusion rates for a concentration of 5,000 nanograms/mL

Example For Dosing Using a Concentration of 5,000 nanograms/mL										
Dosage (nanograms/ kg/ min)	Bodyweight (kg)									
	10	20	30	40	50	60	70	80	90	100
2				1.0	1.2	1.4	1.7	1.9	2.2	2.4
4		1.0	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8
6		1.4	2.2	2.9	3.6	4.3	5.0	5.8	6.5	7.2
8	1.0	1.9	2.9	3.8	4.8	5.8	6.7	7.7	8.6	9.6
10	1.2	2.4	3.6	4.8	6.0	7.2	8.4	9.6	10.8	12.0
12	1.4	2.9	4.3	5.8	7.2	8.6	10.1	11.5	13.0	14.4
14	1.7	3.4	5.0	6.7	8.4	10.1	11.8	13.4	15.1	16.8
16	1.9	3.8	5.8	7.7	9.6	11.5	13.4	15.4	17.3	19.2
	Flow rates in <b>mL/h</b>									

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				1.0	1.1	1.3	1.4	1.6	
6		1.0	1.2	1.4	1.7	1.9	2.2	2.4	
8	1.0	1.3	1.6	1.9	2.2	2.6	2.9	3.2	
10	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0	
12	1.4	1.9	2.4	2.9	3.4	3.8	4.3	4.8	
14	1.7	2.2	2.8	3.4	3.9	4.5	5.0	5.6	
16	1.9	2.6	3.2	3.8	4.5	5.1	5.8	6.4	
	Flow rates in <b>mL/h</b>								

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

## 7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

**8. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

[To be completed nationally]

**10. DATE OF REVISION OF THE TEXT**

[To be completed nationally]

## **LABELLING**

## **PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

### **CARTON box for powder vials and solvent vials:**

**Flolan 0.5 mg powder and solvent for solution for infusion**

**Flolan 1.5 mg powder and solvent for solution for infusion**

### **1. NAME OF THE MEDICINAL PRODUCT**

Flolan 0.5 mg powder and solvent for solution for infusion

Flolan 1.5 mg powder and solvent for solution for infusion

Epoprostenol

### **2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Each vial contains epoprostenol sodium equivalent to 0.5 mg epoprostenol.

Each vial contains epoprostenol sodium equivalent to 1.5 mg epoprostenol.

### **3. 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

This medicine contains sodium: See package leaflet for further information

### **4. PHARMACEUTICAL FORM AND CONTENTS**

Powder and solvent for solution for infusion

Powder for solution for infusion

Solvent for parenteral use

0.5 mg vial powder for solution for infusion, 1 vial of solvent and 1 filter unit

0.5 mg vial powder for solution for infusion, 2 vials of solvent and 1 filter unit

1.5 mg vial powder for solution for infusion, 1 vial of solvent and 1 filter unit

1.5 mg vial powder for solution for infusion, 2 vials of solvent and 1 filter unit

### **5. METHOD AND ROUTE(S) OF ADMINISTRATION**

The powder needs to be reconstituted and diluted before infusion.

Read the package leaflet before use.

Intravenous use

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Use as directed by your physician

**8. EXPIRY DATE**

EXP

Read the package leaflet for the shelf-life of the reconstituted/diluted product

**9. SPECIAL STORAGE CONDITIONS**

*Powder for solution for infusion:*

Store vials below 25°C. Protect from light. Keep dry. Do not freeze. Store in the original package.

*Solvent for parenteral use:*

Store the solvent below 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.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

[See Annex I - To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

**12. MARKETING AUTHORISATION NUMBER(S)**

[To be completed nationally]

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

Medicine subject to medicinal prescription

**15. INSTRUCTIONS ON USE**

[To be completed nationally]

**16. INFORMATION IN BRAILLE**

[To be completed nationally]

**MINIMUM PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING**

**LABEL for solvent vial**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Solvent for parenteral use for Flolan  
Intravenous use

**2. METHOD OF ADMINISTRATION**

Intravenous use  
Read the package leaflet before use.

**3. EXPIRY DATE**

EXP  
Read the package leaflet for the shelf-life of the reconstituted/diluted product

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

Each vial contains 50ml solvent for parenteral use.

**6. OTHER**

**MINIMUM PARTICULARS TO APPEAR ON IMMEDIATE PACKAGING**

**LABEL for powder vial**

**1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION**

Flolan 0.5 mg powder for solution for infusion  
Flolan 1.5 mg powder for solution for infusion  
Intravenous use  
Epoprostenol

**2. METHOD OF ADMINISTRATION**

Intravenous use  
Read the package leaflet before use.

**3. EXPIRY DATE**

EXP  
Read the package leaflet for the shelf-life of the reconstituted/diluted product

**4. BATCH NUMBER**

Lot

**5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT**

Each vial contains 0.5mg epoprostenol (as epoprostenol sodium)  
Each vial contains 1.5mg epoprostenol (as epoprostenol sodium)

**6. OTHER**

**PACKAGE LEAFLET**

## Package leaflet: Information for the user

### **Flolan 0.5 mg Powder and Solvent for Solution for Infusion** **Flolan 1.5 mg Powder and Solvent for Solution for Infusion**

Epoprostenol

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

#### **What is in this leaflet:**

1. What Flolan is and what it is used for
2. What you need to know before you take Flolan
3. How to take Flolan
4. Possible side effects
5. How to store Flolan
6. Contents of the pack and other information

#### **1. What Flolan is and what it is used for**

Flolan contains the active substance epoprostenol which belongs to a group of medicines called prostaglandin, which stops blood from clotting and widens the blood vessels.

Flolan is used to treat a lung condition called ‘pulmonary arterial hypertension’. This is where the pressure is high in the blood vessels in the lungs. Flolan widens the blood vessels to lower the blood pressure in the lungs.

Flolan is used to prevent blood clotting during kidney dialysis when heparin cannot be used.

#### **2. What you need to know before you take Flolan**

##### **Do not take Flolan**

- **if you are allergic** to Flolan or any of the other ingredients of this medicine (listed in section 6).
- if you have **heart failure**.
- if you start to develop a build-up of fluid in your lungs causing breathlessness after starting this treatment.

If you think any of these apply to you, **don’t take Flolan** until you have checked with your doctor.

##### **Warnings and precautions**

Before you are given Flolan your doctor needs to know:

- if you have any problems with **bleeding**.

##### **Skin damage at the injection site**

Flolan is injected into a vein. It is important that the medicine does not leak out of the vein into the surrounding tissue. If it does, the skin could be damaged. The symptoms of this are:

- tenderness
- burning
- stinging
- swelling
- redness.

This may be followed by blistering and shedding of the skin. While you are being treated with Flolan it is important that you check the injection area.

**Contact the hospital** immediately for advice if the area becomes sore, painful or swollen or you notice any blistering or shedding.

### **Effect of Flolan on blood pressure and heart rate**

Flolan can cause your heart to beat faster or slower. Also your blood pressure can become too low. While you are being treated with Flolan your heart rate and blood pressure will be checked. The symptoms of low blood pressure include **dizziness** and **fainting**.

**Tell your doctor** if you get these symptoms. Your dose may need to be reduced or your infusion stopped.

### **Other medicines and Flolan**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Some medicines may affect how Flolan works, or make it more likely that you'll have side effects. Flolan can also affect how some other medicines work if taken at the same time. These include:

- medicines used to **treat high blood pressure**
- medicines used to **prevent blood clots**
- medicines used to **dissolve blood clots**
- medicines to treat **inflammation or pain** (also called 'NSAIDs')
- digoxin (used to treat **heart disease**).

**Tell your doctor or pharmacist** if you are taking any of these.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine as your symptoms could worsen during pregnancy.

**It is not known** whether the ingredients of Flolan can pass into breast-milk. **You should stop breast-feeding your child during treatment with Flolan.**

### **Driving and using machines**

Your treatment may have an effect on the ability to drive or use machinery.

**Don't drive or use machines** unless you're feeling well.

Flolan contains Sodium.

### 3. How to take Flolan

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will decide how much Flolan is right for you. The amount you are given is based on your body weight, and your type of illness. Your dose may be increased or decreased depending on how well you respond to treatment.

Flolan is given by slow infusion (drip) into a vein.

#### **Pulmonary arterial hypertension**

Your first treatment will be given to you in a hospital. This is because your doctor needs to monitor you and find the best dose for you.

You will start with an infusion of Flolan. The dose will be increased, until your symptoms are relieved, and any side effects are manageable. Once the best dose has been found, a permanent tube (line) will be fitted into one of your veins. You can then be treated using an infusion pump.

#### **Kidney dialysis**

You will be given an infusion of Flolan for the duration of your dialysis.

#### **Using Flolan at home (only for treatment of Pulmonary Arterial Hypertension)**

If you are treating yourself at home, your doctor or nurse will show you how to prepare and use Flolan. They will also advise you how to stop treatment if necessary. Stopping Flolan must be done gradually. It is very important that you follow **all** their instructions carefully.

Flolan comes as a powder in a glass vial. Before use, the powder needs to be dissolved in the liquid provided. The liquid does not contain a preservative. If you have any of the liquid left over, it must be thrown away.

#### **Looking after the injection line**

If you have been fitted with a 'line' into a vein it is **very important** to keep this area clean, otherwise you could get an infection. Your doctor or nurse will show you how to clean your 'line' and the area around it. It is very important that you follow all of their instructions carefully.

#### **If you take more Flolan than you should**

**Seek urgent medical attention** if you think you have used or been given too much Flolan. Symptoms of overdose may include headache, nausea, vomiting, fast heart rate, warmth or tingling, or feeling like you might pass out (feeling faint/dizziness).

#### **If you forget to take Flolan**

Do not take a double dose to make up for a forgotten dose.

#### **If you stop taking Flolan**

Stopping Flolan must be done gradually. If the treatment is stopped too quickly you may get serious side effects, including dizziness, feeling weak and breathing difficulties. If you have problems with the infusion pump or injection line that stops, or prevents treatment with Flolan, **contact your doctor, nurse or hospital** immediately.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist or nurse.

#### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately, as these may be signs of infection of the blood or low blood pressure or serious bleeding:

- You feel that your heart is beating faster, or you have chest pain or shortness of breath.
- You feel dizzy or feel faint, especially on standing.
- You have fevers or chills.
- You have more frequent, or longer periods of bleeding.

Talk to your doctor or pharmacist or nurse about any other side effects, including those not listed in this leaflet.

#### Very common side effects

These may affect **more than 1 in 10** people:

- headache
- jaw pain
- pain
- being sick (vomiting)
- feeling sick (nausea)
- diarrhoea
- redness of your face (flushing)

#### Common side effects

These may affect **up to 1 in 10** people:

- infection of the blood (*septicaemia*)
- heart beating faster
- slow heart beat
- low blood pressure
- bleeding at various sites and bruising more easily than normal, for example from the nose or gums
- stomach discomfort or pain
- chest pain
- joint pain
- feeling anxious, feeling nervous
- rash
- pain at the injection site

#### Common side effects that may show up in blood tests

- decrease in the number of blood platelets (cells that help the blood to clot)

#### Uncommon side effects

These may affect **up to 1 in 100** people:

- sweating
- dry mouth

#### Rare side effects

These may affect **up to 1 in 1,000** people:

- infection at the injection site

#### Very rare side effects

These may affect **up to 1 in 10,000** people:

- feeling of tightness around the chest
- feeling tired, weak

- feeling agitated
- pale skin
- redness at the injection site
- overactive thyroid gland
- blockage of the injection catheter

#### **Other side effects**

It is not known how many people are affected:

- build up of fluid in the lungs (pulmonary oedema)
- increase in sugar (glucose) in the blood

### **5. How to store Flolan**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label.

Do not store above 25°C.

Store Flolan in a dry place.

Store in the original outer carton, to protect from light.

Do not freeze.

#### **Pulmonary arterial hypertension**

Once Flolan powder has been dissolved, and diluted, it should ideally be used immediately. If you are being given Flolan using an infusion pump, a 'cold pouch' may be used to maintain the temperature of the solution.

When using a 'cold pouch', the solution can be stored in the pump for up to 24 hours at 2-8°C if necessary. The cold pouch must be regularly changed throughout the day, to maintain the temperature of the solution.

If you are not using a 'cold pouch', the solution can be stored in the pump:

- for up to 12 hours at 25°C, if it has just been made up
- for a maximum of 8 hours if it was made previously and has been stored at 2-8°C.

#### **Renal Dialysis**

Once Flolan has been dissolved and diluted, any unused solution can be stored at 25°C and used within 12 hours.

### **6. Contents of the pack and other information**

#### **What Flolan contains**

The active substance is epoprostenol sodium. Flolan Injection comes in different strengths.

Each vial contains either:

- 0.5 mg epoprostenol sodium
- 1.5 mg epoprostenol sodium.

The other ingredients are Mannitol, Glycine, Sodium Chloride, Sodium Hydroxide and Water.

#### **What Flolan looks like and contents of the pack**

##### ***Injection:***

Flolan is a solution for injection made up of powder and solution. The powder is white or off-white and the solution is clear and colourless.

There are four packs of Flolan available for use in the treatment of pulmonary arterial hypertension, the contents of each pack include:

- One 0.5 mg powder vial and one or two solvent vials and a filter unit.
- One 1.5 mg powder vial and one or two solvent vials and a filter unit.
- One 0.5 mg powder vial.
- One 1.5 mg powder vial.

Not all pack sizes are available in all markets.

### **Marketing Authorisation Holder and Manufacturer**

[See Annex I - To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

**This medicinal product is authorised in the Member States of the EEA under the following names:**

[See Annex I - To be completed nationally]

**This leaflet was last revised in {MM/YYYY}.**

[To be completed nationally]

<-----

The following information is intended for medical or healthcare professionals only:

## **7. INFORMATION FOR HEALTHCARE PROFESSIONALS**

### **Renal Dialysis**

There is only one pack available for use in renal dialysis:

- One 0.5 mg powder vial and one solvent vial

### **Reconstitution:**

1. Use only the solvent provided for reconstitution
2. Withdraw approximately 10mL of the solvent into a sterile syringe, inject it into the vial containing 0.5 mg freeze-dried Flolan powder 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 solvent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanogram per mL Flolan. Only this concentrated solution is suitable for further dilution prior to use. When 0.5 mg Flolan powder is reconstituted with 50 mL of the solvent, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

### **Dilution:**

The concentrated solution is normally further diluted before use. It may be diluted with sodium chloride 0.9% w/v solution, provided a ratio of 6 volumes of sodium chloride 0.9% w/v solution

to 1 volume of concentrated solution is not exceeded e.g. 50 mL of concentrated solution further diluted with a maximum of 300 mL sodium chloride 0.9% w/v solution.

Other common intravenous fluids are unsatisfactory for the dilution of the 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. The filter unit must be used once only and then discarded.

When reconstituted and diluted as directed above, Flolan infusion solutions have a pH of approximately 10 and will retain 90% of their initial potency for approximately 12 hours at 25°C.

Calculation of infusion rate:

The infusion rate may be calculated from the following formula:

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

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

For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile sodium chloride 0.9% w/v solution.

### **Pulmonary arterial hypertension**

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

- One 0.5 mg powder vial and one or two solvent vials and a filter unit.
- One 1.5 mg powder vial and one or two solvent vials and a filter unit.
- One 0.5 mg powder vial.
- One 1.5 mg powder vial.

Not all pack sizes are available in all markets.

Initially, a pack containing solvent must be used. During chronic therapy with Flolan the final concentration of solution may be increased by the addition of a further 0.5 mg or 1.5 mg vial of freeze-dried Flolan.

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

### **Reconstitution:**

1. Use only the solvent provided for reconstitution.
2. Withdraw approximately 10mL of the solvent into a sterile syringe, inject the contents of the syringe into the vial containing Flolan powder 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 solvent and mix thoroughly.

This solution is now referred to as the concentrated solution and contains either 10,000 (for the 0.5 mg strength) or 30,000 nanogram per mL Flolan (for the 1.5 mg strength). Only this concentrated solution is suitable for further dilution prior to use. When 0.5 mg Flolan powder is reconstituted with 50 mL of the solvent, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

**Dilution:**

Flolan may be used either as concentrated solution or in a diluted form for the treatment of pulmonary arterial hypertension. Only the solvent provided may be used for the further dilution of reconstituted Flolan. Sodium chloride 0.9% w/v solution must not be used when Flolan is to be used for the treatment of pulmonary arterial hypertension.

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

The filter must be used once only and then discarded.

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

- 5,000 nanogram/mL – One vial containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.
- 10,000 nanogram/mL – Two vials containing 0.5 mg Flolan reconstituted and diluted to a total volume of 100 mL in solvent.
- 15,000 nanogram/mL – One vial 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:

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

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

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

**Special precautions for storage**

Don't store above 25°C.

Keep container in the outer carton to protect from light.

Keep dry.

Do not freeze.

Any cold pouch used must be capable of maintaining the temperature of the reconstituted solution.

Store between 2 and 8°C for the full administration period.

Reconstitution and dilution should be carried out immediately prior to use.

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