

1. NAME OF THE MEDICINAL PRODUCT

Flolan 0.5 mg Powder and Solvent for Solution for Infusion

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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.

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 in Adults 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. No data is available.

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).

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)
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 ,
Vascular Disorders	
Very common	Facial flushing (seen even in the anaesthetised patient)
Common	Hypotension
Very rare	Pallor
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.	

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.