

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 using 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. See section 4.

What is in this leaflet

1. What Flolan is and what it is used for
2. What you need to know before you use Flolan
3. How to use 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

What Flolan is

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.

What Flolan is used for

- 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 in emergency situations when heparin cannot be used.

2. What you need to know before you use Flolan

Do not use 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 use Flolan** until you have checked with your doctor.

Warnings and precautions

Talk to your doctor before using Flolan:

- if you have any problems with **bleeding**.
- if you are on a controlled sodium diet.

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 using 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 (main component of cooking/table salt)

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

Reconstituted concentrate solution: This medicinal product contains 73 mg of sodium (main component of cooking/table salt) in each vial of concentrated solution. This is equivalent to 4 % of the recommended maximum daily dietary intake of sodium for an adult.

Powder for solution for infusion: This medicinal product contains 3 mg of sodium (main component of cooking/table salt) in each vial of powder for solution. This is equivalent to 0.2 % of the recommended maximum daily dietary intake of sodium for an adult.

Solvent for parenteral use: This medicinal product contains 70 mg of sodium (main component of cooking/table salt) in each vial of solvent. This is equivalent to 4 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Flolan

Always use 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 use 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 use Flolan

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

If you stop using 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 (frequency cannot be estimated from the available data):

- enlarged or overactive spleen
- build up of fluid in the lungs (pulmonary oedema)
- increase in sugar (glucose) in the blood
- swelling due to build up of fluid around the stomach
- too much pumping of blood from the heart leading to shortness of breath, fatigue, swelling of the legs and abdomen due to fluid build-up, persistent cough

Reporting of side effects

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.

You can also report side effects directly via the Yellow Card Scheme Website:

www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

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

For solutions $\leq 150\ 000$ ng/mL:

Freshly prepared Flolan solution (either as a concentrated solution or a further diluted solution) can be administered immediately or stored for a maximum of 8 days at refrigerated conditions (2 to 8 °C), in the medication cassette and used within a maximum time of:

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

For solutions $>150\ 000$ ng/mL and $\leq 300\ 000$ ng/mL:

Reconstituted solutions that have been stored at 2 to 8 °C for up to 7 days can be administered for up to 24 hours at 25 °C.

Freshly prepared reconstituted solutions, or solutions that have been stored at 2 to 8 °C 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.

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 or
- 1.5 mg epoprostenol sodium.

See section 2 for further important information about 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 six 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 solvent vial and a filter unit.
- One 0.5 mg powder vial and two solvent vials and a filter unit.
- One 1.5 mg powder vial and one solvent vial and a filter unit.
- One 1.5 mg powder vial and two solvent vials and a filter unit.
- One 0.5 mg powder vial.
- One 1.5 mg powder vial.

There is only one pack of Flolan available for use in renal dialysis, the contents of each pack include:

- One 0.5 mg powder vial and one solvent vial and a filter unit.

Not all pack sizes are available in all markets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Glaxo Wellcome UK Limited, GSK Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, UK

Manufacturer: GlaxoSmithKline Manufacturing S.p.A., San Polo di Torrile, Parma, Italy

Other formats

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge:

0800 198 5000 (UK Only)

Please be ready to give the following information:

Product name	Flolan 0.5 mg and 1.5 mg injection
Reference number	10949/0310

This is a service provided by the Royal National Institute of Blind People.

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

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DOSAGE AND ADMINISTRATION INFORMATION ONLY

INFORMATION FOR HEALTHCARE PROFESSIONALS

Pulmonary arterial hypertension

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

- One 0.5 mg powder vial and one solvent vial and a filter unit.
- One 0.5 mg powder vial and two solvent vials and a filter unit.
- One 1.5 mg powder vial and one solvent vial and a filter unit.
- One 1.5 mg powder vial and 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, higher concentration solutions may be required. The final concentration of solution may be increased by the addition of further 0.5 mg or 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.

Flolan 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). 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 and 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:

1. Use only the solvent provided for reconstitution.
2. Withdraw approximately 10 mL 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.
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 concentrated solutions are 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 12 and a sodium ion content of approximately 73 mg.

Dilution:

Flolan may be used either as 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.

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.

Epoprostenol 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 of 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.
- 30 000 nanogram/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:

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

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

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.

For additional details of stability following reconstitution, see section 5 ('How to store Flolan').

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

Renal Dialysis

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

- One 0.5 mg powder vial and one solvent vial and a filter unit

Flolan prepared with sterile diluent (pH 12) must not be used with any preparation or administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG). 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

Reconstitution:

1. Use only the solvent provided for reconstitution
2. 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 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 12 and a sodium ion content of approximately 73 mg.

Dilution:

The concentrated solution is normally further diluted immediately prior to use. It may be diluted with sodium chloride 0.9 % w/v (saline) solution, in a ratio of 2.3 volumes of saline to 1 volume of concentrated solution, e.g. 50 mL of concentrated solution further diluted with 117 mL of saline. Other common intravenous fluids are unsatisfactory for the dilution of the concentrated solution as the required pH is not maintained. Flolan solutions are less stable at low pH.

To dilute the concentrated solution, draw it up into a larger syringe and dispense the concentrated solution directly into the chosen infusion solution. Mix well.

The final infusion solution (either as a concentrated solution or a further diluted solution) should be transferred into a suitable container or delivery system prior to administration. A 0.22-micron sterile syringe filter must be used during transfer using firm but not excessive pressure; the typical time taken to for filtration of 50 mL of solution is 70 seconds.

The syringe filter unit must be used only during preparation and then discarded.

When reconstituted and diluted as directed above, Flolan infusion solutions 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.

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