PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed according to a physician's prescription only

Flolan infusion of epoprostenol 500 mcg

The vial of powder contains the active ingredient:

epoprostenol (as sodium) 500 mcg

Flolan infusion of epoprostenol 1500 mcg

The vial of powder contains the active ingredient:

epoprostenol (as sodium) 1500 mcg

For the list of the inactive and allergenic ingredients in the medicine, see section 2 – "Important information about some of the ingredients in the medicine" and section 6 – "Additional information".

Read the leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the physician or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Flolan is used for the long-term intravenous treatment of a lung disease called pulmonary arterial hypertension (PAH) - idiopathic or heritable PAH or PAH associated with connective tissue diseases.

In this lung disease, pressure is high in the blood vessels in the lungs. Flolan widens the blood vessels to lower the blood pressure in the lungs.

Therapeutic group: Anticoagulant (antithrombotic agent), platelet aggregation inhibitor.

Flolan contains the active ingredient epoprostenol which belongs to a group of medicines called prostaglandins. This group of medicines stops blood from clotting and widens the blood vessels.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- you are sensitive (allergic) to the active ingredient (epoprostenol), or to any of the additional ingredients contained in this medicine (listed in section 6).
- you have **heart failure**.
- you 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 physician.

Special warnings regarding use of the medicine

Before the treatment with Flolan, tell the physician if:

- you have any problems with **bleeding**.
- 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 physician** if you get these symptoms. Your dose may need to be reduced or your infusion stopped.

Drug interactions

If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the physician or pharmacist.

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 used to treat **inflammation or pain** (NSAIDs)
• digoxin (used to treat **heart disease**).

→ **Tell your physician 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 physician 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

Treatment with Flolan may have an effect on your ability to drive or use machines.
→ **Do not drive or use machines** unless you're feeling well.

Important information about some of the ingredients in the medicine

Flolan contains **sodium**. To be taken into consideration by patients on a controlled sodium diet.

Reconstituted concentrate solution: This medicinal product contains approximately 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 approximately 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 approximately 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 SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the physician's instructions. Check with the physician or pharmacist if you are uncertain about the preparation dosage and treatment regimen.
The dosage and treatment regimen will be determined by the physician only.
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.
Your first treatment will be given to you in a hospital. This is because your physician 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.

Using Flolan at home

If you are treating yourself at home, your physician 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 solvent provided. The liquid does not contain a preservative. If you have any of the solvent 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 physician 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.

Do not exceed the recommended dose.

If you accidentally have taken a higher dosage

If you have taken or been administered an overdose or if a child has accidentally swallowed some medicine, immediately go to a hospital emergency room and bring the medicine package with you.

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 forgot to take the medicine

If you forget to take the medicine at the required time, do not take a double dose to make up for the forgotten one.

Adhere to the treatment regimen recommended by your physician.

If you stop taking the medicine

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 physician, nurse or hospital immediately.**

Do not take medicines in the dark! Check the label and dose each time you take a medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult the physician or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Flolan may cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not suffer from any of them.

If you experience any of the following symptoms, **tell your physician 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 physician 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:

• 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.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult with the physician.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il/

5. HOW TO STORE THE MEDICINE?

• Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the physician.
• Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
• Do not store above 25˚C.
• Store in a dry place.

- Store in the original outer carton, to protect from light.
- Do not freeze.
- Do not discard medicines in the wastewater or household waste bin. Ask the pharmacist how to dispose of medicines that are no longer in use. These measures will help protect the environment.

Storage conditions of reconstituted solution

The reconstituted solution can be used immediately. Refrigerate at 2°C to 8°C for a maximum period of 8 days if not used immediately.

Freshly prepared reconstituted solution or reconstituted solution that have been stored at 2°C to 8°C for a maximum period of 8 days can be administered up to:

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

Discard any unused solution after this time.

Protect from light. Do not freeze the reconstituted solution.

6. ADDITIONAL INFORMATION

- In addition to the active ingredients, the medicine also contains:

  Powder for solution for infusion:

  Mannitol, glycine, sodium chloride, sodium hydroxide

  Solvent for parenteral use:

  Glycine, sodium chloride, sodium hydroxide, water for injection.

  See section 2 under “Important information about some of the ingredients in the medicine”.
- What the medicine looks like and the contents of the package:

  Flolan is a solution for injection (intravenous). Flolan comes in a vial of white or off-white powder and a vial of clear and colourless solvent.

  Flolan infusion of epoprostenol 500 mcg

  The package contains one powder vial, one solvent vial and a filter unit or one powder vial, two solvent vials and a filter unit.

Flolan infusion of epoprostenol 1500 mcg

The package contains one powder vial, two solvent vials and a filter unit.

Not all package sizes may be marketed.

- License holder: GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.
- Manufacturer: GlaxoSmithKline Manufacturing SpA, Parma, Italy.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:

  Flolan infusion of epoprostenol 500 mcg: 126-72-30642

  Flolan infusion of epoprostenol 1500 mcg: 112-41-29467

Revised in May 2023 according to MoH guidelines.

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

INFORMATION FOR HEALTHCARE PROFESSIONALS

There are three packs available for use, as follows:

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

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 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 concentrated solutions are suitable for further dilution prior to use. When 0.5 mg or 1.5 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 to for filtration of 50mL of solution is 70 seconds.

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

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

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

• 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:

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

Infusion rate (mL/h) = Infusion rate (mL/min) x 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 the medicine').
The solvent contains no preservative; consequently a vial should be used once only and then discarded.

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