Package leaflet: Information for the user

Epoprostenol 0.5 mg Powder and Solvent for Solution for Infusion

Epoprostenol (as sodium)

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.
- 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Epoprostenol is and what it is used for

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

Epoprostenol 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. Epoprostenol widens the blood vessels to lower the blood pressure in the lungs.

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

2. What you need to know before you take Epoprostenol

Do not take Epoprostenol
- **if you are allergic** to Epoprostenol 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 Epoprostenol** until you have checked with your doctor.

Warnings and precautions
Before you are given Epoprostenol your doctor needs to know:
- If you have any problems with bleeding.

Skin damage at the injection site
Epoprostenol 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 Epoprostenol 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 Epoprostenol on blood pressure and heart rate

Epoprostenol can cause your heart to beat faster or slower. Also your blood pressure can become too low. While you are being treated with Epoprostenol 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 Epoprostenol
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines may affect how Epoprostenol works or make it more likely that you'll have side effects. Epoprostenol 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, NSAID's)
- 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 Epoprostenol can pass into breast-milk. **You should stop breast-feeding your child during treatment with Epoprostenol.**

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.

Epoprostenol contains sodium
This medicinal product contains 2.43 mmol (or 56 milligram) sodium (salt) per dose. To be taken into consideration by patients on a controlled sodium (salt) diet.

3. How to take Epoprostenol

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 Epoprostenol 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.

Epoprostenol 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 Epoprostenol. 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 Epoprostenol for the duration of your dialysis.

Using Epoprostenol 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 Epoprostenol. They will also advise you how to stop treatment if necessary. Stopping Epoprostenol must be done gradually. It is very important that you follow **all** their instructions carefully.

Epoprostenol 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 Epoprostenol than you should
Seek urgent medical attention if you think you have used or been given too much Epoprostenol. 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 Epoprostenol
Do not take a double dose to make up for a forgotten dose.

If you stop taking Epoprostenol
Stopping Epoprostenol 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 Epoprostenol, **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.

Other possible side effects include:
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

- Too much pumping of blood form 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. 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

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

5. How to store Epoprostenol

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. The expiry date refers to the last day of that month.

Powder for solution for infusion:
Keep the vial in the outer carton in order to protect from light.
Keep the vial tightly closed in order to protect from moisture.
Store below 25°C

Solvent:
Keep the vial in the outer carton in order to protect from light.
Store below 25°C

Shelf-life after reconstitution:
Pulmonary arterial hypertension
Once Epoprostenol powder has been dissolved, and diluted, it should ideally be used immediately. If you are being given Epoprostenol 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 Epoprostenol has been dissolved and diluted, any unused solution can be stored at 25°C and used within 12 hours.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Epoprostenol contains

Powder for solution for infusion
- The active substance is Epoprostenol (as Sodium).
  1 vial contains 0.531 milligrams Epoprostenol Sodium, corresponding to 0.5 milligrams Epoprostenol.

- The other ingredients are:

Powder for solution for infusion: Mannitol, Glycine, Sodium Chloride, Sodium Hydroxide (for pH adjustment)
Solvent: Glycine, Sodium Chloride, Sodium Hydroxide (for pH adjustment), Water for Injection

When 1 vial with 0.5 mg epoprostenol is reconstituted with 50 ml of sterile buffer, the resultant concentration is 10,000 nanograms per ml.

Solvent
Each vial of solvent contains 50 ml of a sterile glycine buffer solution containing approximately 55 milligram sodium.

What Epoprostenol looks like and contents of the pack

Epoprostenol is a white lyophilised powder cake packed in clear glass vials with grey lyo stopper and aluminium caps with blue flip-off inserts. The solvent is a clear, colourless solution packed in clear glass vials.
After reconstitution Epoprostenol is a colourless solution, practically free of particles.

Each pack unit contains
- one vial Epoprostenol 0.5 mg, containing a white freeze-dried powder cake packed in a 15 ml clear glass vial Type I with grey lyo stopper and aluminium caps with blue flip-off inserts.
- one 50ml sterile Glycine buffer solution, pH 10.5 in a clear glass vial
- one single unit sterile filter device for aseptic preparation of infusion solution

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Mercury Pharmaceuticals Ltd.,
Dashwood House, 69 Old Broad Street, London, EC2M 1QS, United Kingdom

Manufacturer
Prestige Promotion Verkaufsförderung & Werbeservice GmbH
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This medicinal product is authorised in the Member States of the EEA under the following names:

UK:	Epoprostenol 0.5 mg Powder and Solvent for Solution for Infusion
Denmark:	Epoprostenol ”Campuspharma” 500 mikrogram pulver og solvens til infusionsvæske, opløsning
Norway:	Epoprostenol Campuspharma 0,5 mg pulver og væske til infusjonsvæske, oppløsning
Sweden:	Epoprostenol CampusPharma 0,5 mg Pulver och vätska till infusionsvätska, lösning
Germany:	EPOPROSTENOL PANPHARMA 0,5 mg Pulver und Lösungsmittel zur Herstellung einer Infusionslösung

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

Reconstitution and dilution:
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 Epoprostenol 0.5 mg must be carried out using sterile techniques, immediately prior to clinical use.
Reconstitution time should be below 30 seconds.

After reconstitution Epoprostenol is a colourless solution, practically free of particles.

Renal dialysis

Reconstitution:

1. Use only the Glycine Buffer Diluent provided for reconstitution.
2. Withdraw approximately 10 ml of the Glycine Buffer Diluent into a sterile syringe, inject the contents of the syringe into the vial containing 0.5 mg freeze-dried epoprostenol and shake gently until the powder has dissolved.
3. Draw up the resulting epoprostenol solution into the syringe, re-inject it into the remaining volume of the Glycine Buffer Diluent solution and mix thoroughly.

This solution is now referred to as the concentrated solution and contains 10,000 nanograms per ml epoprostenol. Only this concentrated solution is suitable for further dilution prior to use.

When 0.5 mg epoprostenol powder is reconstituted with 50 ml of the Glycine Buffer Diluent, the final injection has a pH of approximately 10.5 and a sodium ion content of approximately 56 mg.

Dilution:
For administration using a pump capable of delivering small volume constant infusions, suitable aliquots of concentrated solution may be diluted with sterile physiological saline.
It may be diluted with physiological saline (0.9%), provided a ratio of 6 volumes of saline to 1 volume of concentrated solution is not exceeded; e.g. 50 ml of concentrated solution further diluted with a maximum of 300 ml saline.

Other common intravenous fluids are unsatisfactory for the dilution of the concentrated solution as the required pH is not attained. Epoprostenol solutions are less stable at low pH.

Prior to using the concentrated solution, or the diluted form, a filtration step is needed. To filter, draw the reconstituted product into a large 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, epoprostenol 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 by the following formula:

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

Infusion rate (ml/hr) = Infusion rate (ml/min) x 60

Infusion rate formulae - examples
When used in renal dialysis Epoprostenol 0.5 mg may be administered as the concentrated solution (a) or in diluted form (b).

a. Using *concentrated solution* i.e. 10,000 ng/ml epoprostenol.

Concentration of solution = 10,000 ng/ml epoprostenol

Dosage (ng/kg/min)	**Bodyweight (kilograms)**							
	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 ml/hr

b. Using concentrated solution, diluted:

10ml *concentrated solution* + 40 ml physiological saline (0.9%). To give a final total volume of 50 ml. Resultant concentration = 2,000 nanograms/ml epoprostenol.

Concentration of solution = 2,000 ng/ml epoprostenol

Dosage (ng/kg/min)	**Bodyweight (kilograms)**							
	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 ml/hr

Primary and secondary Pulmonary Hypertension
The following pack unit is available for use in the treatment of primary pulmonary hypertension:
One vial containing sterile freeze-dried epoprostenol sodium equivalent to 0.5 mg epoprostenol supplied with one 50 ml vial of sterile Glycine Buffer Diluent solution.

Initially a pack unit containing diluent buffer must be used. During chronic epoprostenol 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 epoprostenol.

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 0.5 mg epoprostenol is reconstituted with 50 ml sterile diluent the resultant concentration is 10,000 nanograms per ml.

Dilution:
Epoprostenol 0.5 mg may be used either as concentrated solution or in a diluted form for the treatment of PPH/SPH. Only the Glycine Buffer Diluent provided may be used for the further dilution of reconstituted Epoprostenol 0.5 mg. Physiological saline must not be used when Epoprostenol 0.5 mg is to be used for the treatment of primary pulmonary hypertension.

Concentrations commonly used in the treatment of primary or secondary pulmonary hypertension are as follows:

- 15,000 ng/ml – 3vials of 0.5mg epoprostenol or one vial of 1.5mg epoprostenol reconstituted and diluted to a total volume of 100ml in the Glycine Buffer Diluent.
- 10,000 ng/ml – two vials containing 0.5mg epoprostenol reconstituted and diluted to a total volume of 100ml in the Glycine Buffer Diluent.

The maximum recommended concentration for administration in primary pulmonary hypertension is 60,000ng/ml.

Epoprostenol 0.5 mg must not be administered with other parenteral solutions or medications when used for primary or secondary pulmonary 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 pump cassette using firm but not excessive pressure; the typical time taken for filtration of 50 ml of concentrated solution is 70 seconds.

Remove the filter from the syringe and draw up the additional volume of the Glycine Buffer Diluent required to achieve the desired dilution.

Refit the filter to the syringe and dispense the additional buffer through this into the concentrated Epoprostenol 0.5 mg solution in the cassette.

Mix well.
The filter unit must be used for the dilution of one pack only and then discarded.

The ambulatory pump used to administer Epoprostenol 0.5 mg should (1) be small and lightweight, (2) be able to adjust infusion rates in ng/kg/min increments, (3) have occlusion, end of infusion, and low battery alarms, (4) be accurate to ± 6% of the programmed rate (5) be positive pressure driven (continuous or pulsatile) with intervals between pulses not exceeding 3 minutes at infusion rates used to deliver Epoprostenol 0.5 mg, and (6) include a cold pouch system. The reservoir should be made of polyvinyl chloride, polypropylene, or glass.
Protect infusion bags from light during infusion.

CALCULATION OF INFUSION RATE:
The infusion rate may be calculated from the formula given above for renal dialysis.

An example of a concentration commonly used in primary or secondary pulmonary hypertension is shown below.

Infusion rates for a concentration of 15,000 nanograms/ml:

Concentration of solution = 15,000 ng/ml epoprostenol

Dosage (ng/kg/min)	**Bodyweight (kilograms)**							
	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 ml/hr