PACKAGE LEAFLET

Package leaflet: Information for the patient

Epoprostenol 0.5 mg powder for solution for infusion
Epoprostenol 1.5 mg powder 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, 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, pharmacist or nurse. 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 prostaglandins, which stop blood from clotting and widen 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 also 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 Epoprostenol

Do NOT use 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 use** Epoprostenol until you have checked with your doctor.

Warnings and precautions

Talk to your doctor before treatment with Epoprostenol
- if you **bleed** easily (for example from your nose).

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 of the skin.

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

Children and adolescents
The safety and efficacy of Epoprostenol in children have not yet been established.

Other medicines and Epoprostenol
Tell your doctor or nurse if you are using, have recently used or might use 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 'NSAIDs'), for example ibuprofen
- digoxin (used to treat **heart disease**).

Tell your doctor or nurse 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 treatment with this medicine.

It is not known whether the ingredients of Epoprostenol can pass into breast-milk. **You should stop breastfeeding 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 **if you're feeling unwell**.

Epoprostenol contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

The diluted solution of Epoprostenol (pH 12) must not be used with administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG).

3. How to use Epoprostenol

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

Epoprostenol comes as a powder in a small glass vial. The powder needs to be dissolved before use. Epoprostenol should not be given as a quick injection into your vein. It should always be given as an intravenous infusion (drip).

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 a liquid. 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. It is also **very important** that you carefully follow all instructions regarding the change of the pump drug delivery reservoir (cassette) and that you always use an extension set with an in-line filter, as instructed by your doctor **to reduce the risk of an infection**.

If you use 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 use Epoprostenol
Do not use a double dose to make up for a forgotten dose.

If you stop using 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 an 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, 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 if you get any of the following signs of infection of the blood, 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, for example nose bleeding
- The injection site becomes sore, painful or swollen or you notice any blistering or shedding of the skin (see Section 2).

Other possible side effects

Very common (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 (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
- decrease in the number of blood platelets (cells that help the blood to clot). This may show up in blood tests.

Uncommon (may affect up to 1 in 100 people)
- sweating
- dry mouth.

Rare (may affect up to 1 in 1000 people)
- infection at the injection site.

Very rare (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.

Not known (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, 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 at: 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 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 vial label and carton after EXP. The expiry date refers to the last day of that month.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.

The reconstituted solution should be further diluted to the final concentration within one hour of reconstitution (see *Information intended for medical or healthcare professionals*).
For storage conditions after reconstitution and dilution of the medicine see *Information intended for medical or healthcare professionals*.

Do not use this medicine if you notice any particles in the reconstituted solution.

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 protect the environment.

6. Contents of the pack and other information

What Epoprostenol contains

Epoprostenol 0.5 mg, powder for solution for infusion:
- The active substance is epoprostenol (as epoprostenol sodium).
  Each vial contains 0.531 mg epoprostenol sodium equivalent to 0.5 mg epoprostenol.
  One ml of reconstituted solution contains 0.1 mg epoprostenol (as epoprostenol sodium).

Epoprostenol 1.5 mg, powder for solution for infusion:
- The active substance is epoprostenol (as epoprostenol sodium).
  Each vial contains 1.593 mg epoprostenol sodium equivalent to 1.5 mg epoprostenol.
  One ml of reconstituted solution contains 0.3 mg epoprostenol (as epoprostenol sodium).

The other ingredients are glycine, sucrose and sodium hydroxide (for pH adjustment).

What Epoprostenol looks like and contents of the pack

White to off-white powder in a clear glass vial with a rubber stopper and an aluminium flip-off cap.

Each pack contains one vial holding 0.5 mg powder.
Each pack contains one vial holding 1.5 mg powder.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Sun Pharmaceutical Industries Europe B.V.
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Italy	Epoprostenolo SUN
Netherlands	Epoprostenol SUN
Spain	Epoprostenol SUN
United Kingdom (Northern Ireland)	Epoprostenol

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

Renal dialysis

There is one pack available for use in the treatment of renal dialysis, as follows:

- One 0.5 mg powder vial.

Reconstitution:

Withdraw 5 ml of either sterile water for injection or sodium chloride 0.9% injection diluent into a sterile syringe, inject the contents of the syringe into the vial containing Epoprostenol and shake gently until the powder has dissolved. The reconstituted solution should be examined prior to further dilution. Its use is forbidden in the presence of discolouration or particles. Any unused reconstituted solution should be disposed of in accordance with local requirements.

Dilution:

The reconstituted solution should be further diluted to the final concentration within one hour of reconstitution. Further dilution should be performed with the same diluent as used for reconstitution of the sterile, lyophilised powder.

When the Epoprostenol lyophilisate is reconstituted with sterile water for injection or sodium chloride 0.9% injection diluent, the final injection solution has a pH comprised between 11.5 and 12.

Calculation of infusion rate:

Infusion rates may be calculated using the following formula:

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

Infusion rate (ml/h) = Infusion rate (ml/min) × 60

Pulmonary arterial hypertension

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

- One 0.5 mg powder vial.
- One 1.5 mg powder vial.

Reconstitution:

Withdraw 5 ml of either sterile water for injection or sodium chloride 0.9% injection diluent into a sterile syringe, inject the contents of the syringe into the vial containing Epoprostenol and shake gently until the powder has dissolved. The reconstituted solution should be examined prior to further dilution. Its use is forbidden in the presence of discolouration or particles. Any unused reconstituted solution should be disposed of in accordance with local requirements.

Dilution:

The reconstituted solution should be further diluted to the final concentration within one hour of reconstitution. Further dilution should be performed with the same diluent as used for reconstitution of the sterile, lyophilised powder. Epoprostenol when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump.

When the Epoprostenol lyophilisate is reconstituted with sterile water for injection or sodium chloride 0.9% injection diluent, the final injection solution has a pH comprised between 11.5 and 12.

Suitable ambulatory pumps to be used for the administration of Epoprostenol include:

- CADD-Legacy 1
- CADD-Legacy PLUS

Manufactured by Smiths Medical.

Pump accessories found to be compatible with the administration of Epoprostenol include:

- CADD disposable Medication Cassette Reservoir 50 mL; 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.

Only extension sets with an in-line 0.22 micron filter placed between the infusion pump and the catheter must be used. It is recommended to use filters with a hydrophilic polyethersulfone membrane. The extension set and the in-line filter must be changed at least every 48 hours.

The diluted solution of Epoprostenol (pH 12) must not be used with administration materials containing polyethylene terephthalate (PET) or polyethylene terephthalate glycol (PETG).

The vial containing 0.5 mg epoprostenol must be used for the preparation of solutions with final concentrations below 15,000 ng/mL.

Table 1 provides examples for preparing frequently used concentrations of Epoprostenol solutions. Each vial is for single use only.

Table 1: Frequently used concentrations - Examples of reconstitution and dilution

Final Concentration (ng/ml)	**Directions:**
3000 ng/ml	Dissolve contents of one 0.5 mg vial with 5 ml of either sterile water for injection or sodium chloride 0.9% injection. Withdraw 3 ml of the vial contents and add to a sufficient volume of the identical diluent to make a total of 100 ml.
5000 ng/ml	Dissolve contents of one 0.5 mg vial with 5 ml of either sterile water for injection, or sodium chloride 0.9% injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 ml.
10,000 ng/ml	Dissolve contents of two 0.5 mg vials, each with 5 ml of either sterile water for injection or sodium chloride 0.9% injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 ml.
15,000 ng/ml*	Dissolve contents of one 1.5 mg vial with 5 ml of either sterile water for injection or sodium chloride 0.9% injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 ml.
30,000 ng/ml*	Dissolve contents of two 1.5 mg vials, each with 5 ml of either sterile water for injection or sodium chloride 0.9% injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 100 ml.
30,000 ng/ml*	Dissolve contents of one 1.5 mg vial with 5 ml of either sterile water for injection or sodium chloride 0.9% injection. Withdraw entire vial contents and add to a sufficient volume of the identical diluent to make a total of 50 ml.
* Solutions with higher final concentrations may be necessary for patients who receive long-term administration of Epoprostenol.	

Epoprostenol diluted to the final concentration in the drug delivery reservoir as directed can be administered immediately at room temperature (25ºC) or, if stored, for up to 8 days at 2 to 8ºC as per the conditions of use outlined in Table 2.

Table 2: Maximum duration of administration (hours) at room temperature (25ºC) of fully diluted solutions stored in the drug delivery reservoir

Final concentration range	**Immediate administration***	**If stored for up to 8 days at 2 to 8ºC***
≥ 3000 ng/ml and <15,000 ng/ml	48 hours	24 hours
≥ 15,000 ng/ml	48 hours	48 hours

Do not expose the fully diluted solution to direct sunlight.

Special precautions for storage

Do not freeze.

The reconstituted solution should be further diluted to the final concentration within one hour of reconstitution.
Reconstitution and dilution should be carried out immediately prior to use.

Freshly prepared epoprostenol diluted solutions for the treatment of pulmonary arterial hypertension can be administered immediately at 25°C, or stored in the drug delivery reservoir in order to protect from light for up to 8 days at 2 to 8°C as per the conditions of use outlined in Table 2.