Package leaflet: Information for the user

Iloprost 100 micrograms/ml concentrate for solution for infusion

(as iloprost trometatmol)

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 Iloprost is and what it is used for

The name of this medicine is Iloprost 100 micrograms / ml concentrate for solution for infusion called Iloprost throughout this leaflet. It contains the active ingredient iloprost which imitates a natural substance in the body called prostacyclin. Iloprost and prostacyclin prevent unwanted blockages or narrowing of blood vessels and allow improved blood flow in the arteries.

Iloprost promotes the healing of wounds caused by insufficient blood flow (ischemia) by providing better oxygenation, and relieving pain in severe, chronic disorders of the blood circulation.

Iloprost is used in adults in the treatment of:
- Severe chronic ischaemia of lower limbs (decreased blood supply) in patients at risk of amputation, in whom surgical revascularisation or angioplasty (repair of the blood vessel) has failed or is not indicated, following the meeting of physicians, surgeons and radiologists.
- Severe Raynaud's phenomena (reduced blood flow to fingers and toes) in patients with progressive trophic disorders.

2. What you need to know before you use Iloprost

Do not use Iloprost if you:
- are **allergic** to iloprost or any of the other ingredients of this medicine (listed in section 6).
- are at **increased risk of bleeding** – for example if you have a gastric (stomach) or duodenal ulcer, bleeding from wounds or had bleeding inside the skull.
- have **suspected fluid build-up in the lungs** (pulmonary oedema) accompanied by difficulty in breathing.
- had a **heart attack** within the last six months.
- have an **irregular heart rate** (arrhythmias).
- have **poor blood flow** to the heart muscle (severe coronary artery disease or unstable angina).
- are suffering with **angina or chest pain**
- had an acute or chronic congestive heart failure.
- have congenital or acquired valvular defects with clinical relevant myocardial function disorders not related to pulmonary hypotension.
- had a **stroke** in the past three months.
- are **pregnant or breast-feeding** (see 'Pregnancy, breast-feeding and fertility').

If you think that any of the above applies to you, talk to your doctor.

Warnings and precautions
Talk to your doctor before Iloprost is given to you if you:
- require **urgent amputation**. Surgery should not be delayed if you need urgent amputation (e.g. in case of infected gangrene).
- are a **smoker**. You should stop smoking.
- have **liver problems or severe kidney problems**, tell your doctor. You may be prescribed a lower dose of Iloprost and your doctor will monitor closely.
- have **low blood pressure**, care should be taken so as not to further reduce blood pressure (hypotension).
- have **severe heart disease**, you will be monitored closely.

After administration, **when moving from a lying to upright position**, your blood pressure may fall. This can make you feel dizzy for a while until your blood pressure returns to normal values (this is called 'orthostatic hypotension'). Stand up slowly when you get out of bed. This will help your body get used to this change in position and blood pressure.

If undiluted Iloprost is infused in the veins, this may lead to local changes at the injection site due to extravasation.

If Iloprost comes into contact with your skin or eyes:
This medicine should not come into contact with your skin or eyes. On contact with the skin, iloprost may cause long-lasting but painless redness of the skin (erythema). In the event of such contact, wash immediately the skin or the eyes with water or saline.

Children and adolescents
The safety and efficacy of iloprost in children aged up to 18 years have not been established.

Other medicines and Iloprost
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. Iloprost and some other medicines may affect each other in the way they work in your body. Tell your doctor if you are taking:
- **Medicines used to treat high blood pressure or heart disease**. Your blood pressure may drop much further. Tell your doctor if you are taking any of these. He/she may change the dose of Iloprost you are given.
- **Medicines that thin the blood or inhibit blood clotting** (e.g. Aspirin or Acetylsalicylic acid, ticlopidine, clopidogrel) The risk of bleeding

may be increased. If you suffer bleeding, treatment with Iloprost should be discontinued.

Pregnancy, breast-feeding and fertility
Iloprost is not indicated for pregnant or breastfeeding women.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before this medicine is given to you.
This medicine must not be used during pregnancy or while breast-feeding.
Women of childbearing potential have to use effective contraception during treatment.

Driving and using machines
Iloprost lowers blood pressure and may cause dizziness or light-headedness in some people.
Do not drive or operate any tools or machines if you feel these effects.

Important information about some of the ingredients of Iloprost
Ethanol This medicine contains 8.10 mg of alcohol (ethanol) in each ml of the concentrate. The small amount of alcohol in this medicine will not have any noticeable effects.
This medicine contains 7.08 mg sodium in 1 ml of the concentrate, that is to say essentially "sodium-free".

3. How to use Iloprost

Iloprost should only be used under strict monitoring in hospitals or in out-patient clinics with adequate facilities.

How Iloprost is prepared for administration
Iloprost concentrate for solution for infusion is **NOT** ready to use and requires dilution before administration.
Iloprost is a solution contained in a glass ampoule. The content of the ampoule is diluted with physiological saline solution or a 5% glucose solution. The infusion should be prepared just before it is administered to ensure sterility.
The content of the ampoule and the diluent must be mixed thoroughly. Iloprost must be used only after dilution. For further information for physicians or healthcare professionals on the preparation of the dilution see section "The following information is intended for medical and healthcare professionals only" at the end of this leaflet.

How Iloprost is given
The solution is infused intravenously with a venous catheter directly into one of the veins in your arm or into a central intravenous catheter inserted into a vein near your neck.
Iloprost is administered as infusion over 6 hours daily.
The dose is adjusted according to individual tolerability within the range of 0.5 to 2.0 nanograms iloprost/kg body weight/min. iloprost/kg/min.
Your blood pressure and heart rate will be measured at the start of the infusion and after every dose increase.

How much Iloprost is given
During the first 2 to 3 days, the individually tolerated dose is established. For this purpose, your doctor will start the treatment at a low dose. Treatment should be started at an infusion rate of 0.5 nanograms/kg/min for 30 minutes. The dose should then be increased at intervals of 30 minutes in steps of 0.5 nanograms/kg/min up to a maximum of 2.0 nanograms/kg/min. The exact infusion speed should be calculated on the basis of body weight to reach an infusion within the range of 0.5 to 2.0 nanograms/kg/min.
If adverse effects occur, such as headache and nausea or an undesirable drop in blood pressure, tell your doctor immediately. The infusion rate should be reduced until the tolerable dose is found. If the adverse effects are severe, the infusion should be interrupted. For the remaining duration, the treatment should be continued with the dose found to be tolerated in the first 2 to 3 days.
The doctor will determine whether Iloprost will be infused intravenously by an infusion pump or with an injector. If Iloprost is administered

The following information is intended for medical and healthcare professionals only

Iloprost concentrate for solution for infusion is **NOT** ready to use and requires dilution before administration. The following sections provide more information to your doctor when using and infusion pump or a syringe driver for the administration of Iloprost.

Infusion rates (ml/hour) for different doses using an infusion pump

In general, the ready-to-use infusion solution is infused intravenously by means of an infusion pump (e.g. Infusomat®).

In case of an Iloprost 100 micrograms/ml concentration of 0.2 micrograms/ml, the required infusion rate should be determined according to the below described scheme to reach a dose within the range of 0.5 to 2.0 nanograms/kg/min.

The following table (Table 1) can be used to calculate the infusion rate corresponding to the individual weight of the patient and the dose to be infused. Match the patient's actual weight on the table, then set the infusion rate based on the desired dose in nanograms/kg/min.

Table 1: Infusion rates [ml/h] for different doses when using an infusion pump.

Body weight [kg]	Dose [nanograms/kg/min]			
	0.5	1.0	1.5	2.0
	Infusion rate [ml/h]			
40	6.0	12	18.0	24
50	7.5	15	22.5	30
60	9.0	18	27.0	36
70	10.5	21	31.5	42
80	12.0	24	36.0	48
90	13.5	27	40.5	54
100	15.0	30	45.0	60
110	16.5	33	49.5	66

Infusion rates (ml/hour) for different doses using an syringe driver

A syringe driver with a 50 ml injection syringe (e.g.Perfusor®) may also be used to infuse Iloprost 100 micrograms/ml.

In case of an Iloprost 100 micrograms/ml concentration of 0.2 micrograms/ml, the required infusion rate must be determined according to the below described scheme, to reach a dose within the range of 0.5 to 2.0 nanograms/kg/min.

with an infusion pump, it will be diluted before infusion to a final concentration of 0.2 micrograms/ml. If Iloprost is administered with an injector, it will be diluted before infusion to a final concentration of 2 micrograms/ml.

Patients with kidney or liver problems
If you have kidney problems requiring dialysis or liver cirrhosis, iloprost elimination is reduced and a dose reduction (e.g. half the recommended dose) is necessary. Tell your doctor if you have problems with your liver or kidneys.

How long Iloprost is given
The duration of the treatment is up to 4 weeks.
The safety and efficacy of Iloprost has not been studied for treatment for longer than 4 weeks or after repetitive cycles.

Continuous infusion over several days is not recommended, because it can lead to reduced effect on platelets and increased platelet aggregation (platelet hyperaggregability) at the end of treatment. No clinical complications associated with these phenomena have been reported.

If you feel that the effect of Iloprost is too strong or too weak, tell your doctor.

If you are given more Iloprost than you should
Drop in blood pressure (hypotensive reaction) can be expected, as well as headache, redness of the face (flushing), nausea, vomiting and diarrhoea. An increase in blood pressure, reduced or increased heart rate and limb or back pain may also occur.
No specific antidote is known.
In case of overdose, your doctor is advised to discontinue infusion of iloprost, to monitor you and treat your symptoms.

If you stop the treatment with Iloprost
If the infusion therapy with Iloprost is discontinued, your doctor will take care to restore the changes that might have been made to other medicines you take, due to Iloprost administration (e.g. dose reductions).

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.

The most severe side effects which have been reported as having a fatal or life-threatening effect in patients taking iloprost are:
- Cerebrovascular event (stroke),
- Myocardial infarction (heart attack)
- Pulmonary embolism (difficulties breathing or chest pain when breathing due to blood clot in the lung),
- Heart failure,
- Convulsions (fits),
- Hypotension (abnormally low blood pressure)
- Tachycardia (fast heart rate)
- Asthma,
- Angina pectoris (chest pain or discomfort due to insufficient blood flow to the heart)
- Dyspnoea (difficulty breathing)
- Pulmonary oedema (difficulty breathing or coughing blood due to fluid build-up in the lung).

The most common side effects observed in patients taking Iloprost include headache, flushing (redness of the face), hyperhidrosis (sweating) and gastrointestinal symptoms, such as nausea and vomiting. These side effects are likely to occur during the dose titration at the start of treatment to identify the best tolerable dose for the individual patient. However, all these side effects usually disappear quickly with dose reduction.

Possible side effects are listed below according to their frequency.

Common (may affect up to 1 in 10 people):
- Decreased appetite.
- Apathy
- Confused state
- Dizziness/vertigo (feeling of spinning)
- Paraesthesia (numbness and tingling) / palpitations/ hyperaesthesia (increased sensitivity to pain or touch)
- Agitation
- Drowsiness
- Tachycardia (fast heart rate)
- Bradycardia (slow heart rate)
- Angina pectoris (chest pain or discomfort due to insufficient blood flow to the heart)
- Hypotension (abnormally low blood pressure)
- Blood pressure increased
- Dyspnoea (difficulty breathing)
- Diarrhoea
- Abdominal discomfort/abdominal pain
- Pain in jaw pain/ trismus (jaw spasm, locking jaw)
- Myalgia (muscle pain)/ arthralgia (joint pain)
- Pain
- Fever, body temperature increased
- Burning sensation
- Asthenia (weakness)/ malaise (feeling of major weakness)
- Chills
- Thirst
- Infusion site reactions such as infusion of site erythema, infusion site pain or infusion site phlebitis (vein irritation)

Uncommon (may affect up to 1 in 100 people):
- Thrombocytopenia (blood disorder characterized by easy bruising or bleeding)
- Hypersensitivity (allergy)
- Anxiety, depression, hallucinations
- Syncope (short loss of consciousness)
- Tremor (trembling or shaking)
- Migraine
- Blurred vision
- Eye irritation
- Eye pain
- Arrhythmia/extrasystoles (abnormal heart rate)
- Deep vein thrombosis (pain in the legs due to a blood clot in the blood vessels of the legs)
- Haemorrhagic diarrhoea (diarrhoea with blood in stools)
- Rectal haemorrhage
- Dyspepsia (heartburn or stomach pain)
- Rectal tenesmus (pain due to constipation)
- Constipation
- Dysphagia (difficulty swallowing)
- Dry mouth
- Dyspepsia (sense of taste disorder)
- Liver disorder (hepatic impairment)
- Jaundice (yellowing of the skin and white of the and/or itching due to hepatic disorder)
- Pruritus (itching)
- Tetany (prolonged painful muscle spasm), muscle spasms
- Hypertonia (increased muscle tension)
- Kidney pain

- Vesical tenesmus (failed urinary urgency)
- Abnormal urine
- Dysuria (painful urination or difficult urinating)

Rare (may affect up to 1 in 1,000 people):
- Cough
- Proctitis (rectal irritation)

Iloprost may cause chest pain or discomfort due to angina pectoris, especially in patients with coronary disease.

The risk of bleeding is increased in patients when inhibitors of platelet aggregation, heparin or anticoagulants of the coumarin type are given concomitantly.

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 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 Iloprost

Keep this medicine out of the sight and reach of children.
Store in the original packaging.
Do not freeze.
After opening and dilution; chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the product should be used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8 °C, unless the dilution has taken place in controlled and validated aseptic conditions.

Do not use this medicine after the expiry date which is stated on the carton and ampoule label, after EXP. The expiry date refers to the last day of that month.

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 Iloprost contains
- The active substance is iloprost. Each ampoule contains 0.5 ml concentrate for solution for infusion containing 50 micrograms Iloprost (as Iloprost trometamol). Each 1 ml of concentrate for solution for infusion contains 100 micrograms Iloprost (as Iloprost trometamol).
- The other ingredients are, trometamol, ethanol 96%, sodium chloride, hydrochloric acid dilute (as pH adjusting agent), water for injection.

What Iloprost looks like and contents of the pack
Clear and colourless solution free of visible particles.
Clear Type I glass 1 ml ampoule, in a PVC blister and paper folding carton.
Pack sizes: 1 ampoule and 5 ampoules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Zentiva Pharma UK Limited, 12 New Fetter Lane, London, EC4A 1JP, UK

Manufacturer
Zentiva, k.s., U kabelovny 130, Dolní Měcholupy,
102 37, Prague 10, Czech Republic

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The following table (Table 2) can be used to calculate the infusion rate corresponding to the individual weight of the patient and the dose to be infused. Match the patient's actual weight on the table, then set the infusion rate based on the desired dose in nanograms/kg/min.

Table 2: Infusion rates [ml/h] for different doses when using an syringe driver.

Body weight [kg]	Dose [nanograms/kg/min]			
	0.5	1.0	1.5	2.0
	Infusion rate [ml/h]			
40	0.60	1.2	1.80	2.4
50	0.75	1.5	2.25	3.0
60	0.90	1.8	2.70	3.6
70	1.05	2.1	3.15	4.2
80	1.20	2.4	3.60	4.8
90	1.35	2.7	4.05	5.4
100	1.50	3.0	4.50	6.0
110	1.65	3.3	4.95	6.6

Due to possible interactions, no other medicinal product should be added to the ready-to-use solution for infusion.

In order to ensure sterility, the ready-to-use solution should be prepared every day.

Instructions on handling

The ampoule contents and diluent must be thoroughly mixed.

Dilution of Iloprost 100 micrograms/ ml with an infusion pump.

Iloprost solution at concentration level 0.2 micrograms/ml in 5 % glucose should not be prepared into plastic bottles, it can be prepared into glass bottles or infusion bags.

The iloprost infusion solution at concentration level 0.2 micrograms/ml in saline solution can be prepared in plastic and glass bottles or in infusion bags.

The contents of an ampoule is 0.5 ml of Iloprost 100 micrograms/ ml (i.e. 50 micrograms) is diluted with 250 ml 0.9% Sodium Chloride Infusion or a 5% Glucose Infusion respectively.

Dilution of Iloprost 100 micrograms/ ml with an infusion syringe pump.

The contents of an ampoule is 0.5 ml of Iloprost 100 micrograms/ ml (i.e. 50 micrograms) is diluted with 25 ml 0.9% Sodium Chloride Infusion or a 5% Glucose Infusion respectively.