Package leaflet: Information for the user

Iloprost 100 micrograms/ml Concentrate for solution for infusion

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.
- The full name of this medicine is Iloprost 100 micrograms/ml Concentrate for solution for infusion but within the leaflet it will be referred to as Iloprost 100 micrograms/ml.

What is in this leaflet

1. What Iloprost 100 micrograms/ml is and what it is used for

Iloprost 100 micrograms/ml contains the active ingredient iloprost which imitates a natural substance in the body called prostacyclin. Iloprost 100 micrograms/ml and prostacyclin prevent unwanted blockages or narrowing of blood vessels and allow improved blood flow in the arteries.

Iloprost 100 micrograms/ml 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 100 micrograms/ml 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 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 100 micrograms/ml

Do not use Iloprost 100 micrograms/ml if you:

- have **hypersensitivity (allergy)** to iloprost or any of the other ingredients of this medicine (listed in section 6 “Contents of the pack and other information”)
- are at **increased risk of bleeding** – for example, if you have an active 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**
- 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 clinically relevant myocardial function disorders not related to pulmonary hypertension
- had a **stroke** in the past 3 months
- are **pregnant or breast feeding**

Warnings and precautions

Talk to your doctor before using Iloprost 100 micrograms/ml 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 100 micrograms/ml and your doctor will monitor you 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 100 micrograms/ml is infused in the veins this can lead to local changes at the injection site due to extravasation.

If Iloprost 100 micrograms/ml comes into contact with your skin:
Iloprost 100 micrograms/ml solution 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.

This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per dose.

Other medicines and Iloprost 100 micrograms/ml

Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Iloprost 100 micrograms/ml and some other medicines may affect each other in the way they work in your body. Take special care to mention any of the following:

- **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 100 micrograms/ml you should take.
- **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 from bleeding, treatment with Iloprost 100 micrograms/ml should be discontinued.

Pregnancy, breast-feeding and fertility:

Iloprost 100 micrograms/ml is not indicated for pregnant or breast-feeding 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 using this medicine. Women of childbearing potential have to use effective contraception during treatment.

Driving and using machines:

Iloprost 100 micrograms/ml 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.

3. How to use Iloprost 100 micrograms/ml

Iloprost 100 micrograms/ml should be used only under strict monitoring in hospitals or out-patient clinics with adequate facilities.

How Iloprost 100 micrograms/ml is prepared for administration

Iloprost 100 micrograms/ml is a solution contained in a glass ampoule. The content of the ampoule is diluted with 0.9% physiological sodium chloride solution or a 5% glucose solution. The infusion solution should be prepared just before the infusion daily, to ensure sterility. The content of the ampoule and the diluent must be mixed thoroughly. Iloprost 100 micrograms/ml 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 100 micrograms/ml 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 100 micrograms/ml 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 ng iloprost/kg body weight/min. Your blood pressure and heart rate will be measured at the start of the infusion and after every dose increase.

How much Iloprost 100 micrograms/ml **is given**

During the first 2-3 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 ng/kg/min for 30 minutes. The dose should then be increased at intervals

of 30 minutes in steps of 0.5 ng/kg/min up to 2.0 ng/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 ng/kg/min (see tables below for use with infusion pump or syringe driver).

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 100 micrograms/ml will be infused intravenously by an infusion pump or with syringe driver. If Iloprost 100 micrograms/ml is administered with an infusion pump, it will be diluted before infusion to a final concentration of 0.2 micrograms/ml. If Iloprost 100 micrograms/ml is administered with a syringe driver, it will be diluted before infusion to a final concentration of 2 micrograms /ml.

If you have renal failure 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 100 micrograms/ml is given:

The duration of treatment is up to 4 weeks.

The safety and efficacy of Iloprost 100 micrograms/ml have not been studied for treatment longer than 4 weeks or after repetitive treatment 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 100 micrograms/ml is too strong or too weak, tell your doctor or pharmacist.

If you have any further questions about the use of this product, ask your doctor or pharmacist.

If you use more Iloprost 100 micrograms/ml 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 using Iloprost 100 micrograms/ml:

If the infusion therapy with Iloprost 100 micrograms/ml is discontinued, your doctor will take care to restore the changes that might have been made to other medicines you take, due to Iloprost 100 micrograms/ml administration (e.g. dose reductions).

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
- 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 buildup in the lung)

The most common side effects observed in patients taking Iloprost 100 micrograms/ml 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
- Confusional state
- Dizziness/vertigo (feeling of 'spinning')
- Paraesthesia (numbness and tingling)/palpitations/hyperesthesia (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/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
- Fatigue
- Thirst
- Infusion site reactions such as infusion 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, hallucination
- 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 eye 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 difficulty urinating)

Rare (may affect up to 1 in 10,000 people)

- Cough
- Proctitis (rectal irritation)

Iloprost may cause chest pain or discomfort due to angina pectoris, especially in patients with coronary artery 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 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 Iloprost 100 micrograms/ml

Keep this medicine out of the sight and reach of children.
This medicinal product does not require any special storage conditions.
After opening and dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 25ºC. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8ºC, 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. The expiry date refers to the last day of that month.
Do not dispose of medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Iloprost 100 micrograms/ml contains:

- The active substance is iloprost
  1 ml of Iloprost 100 micrograms/ml contains 100 micrograms of iloprost (equivalent to 134 micrograms iloprost trometamol).

- The other ingredients are: trometamol, ethanol 96% (v/v), sodium chloride, hydrochloric acid for pH adjustment and water for injection.

What Iloprost 100 micrograms/ml looks like and contents of the pack

- Iloprost 100 micrograms/ml is a clear colourless solution, free of visible particles which is diluted prior to infusion via a vein. It is supplied in glass ampoules.
- Iloprost 100 micrograms/ml is available in the following pack sizes:

1 Box of 1 or 5 ampoules, each with 0.5 ml concentrate for solution for infusion or 1 box of 1 or 5 ampoules, each with 1 ml concentrate for solution for infusion.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Colonis Pharma Ltd
25 Bedford
Bloomsbury
London
WC1B 3HH
United Kingdom

Manufacturer
Rafarm S.A.
Thesi Pousi-Xatzi
Agiou Louka
19002, Paiania Attiki
Greece

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The following information is intended for medical and healthcare professionals only:
Iloprost 100 micrograms/ml should be used only after dilution. The following sections provide more information to your doctor when using an infusion pump or a syringe driver for the administration of Iloprost 100 micrograms/ml.

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 ng/kg/min.

The following table 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 body weight on the table, then set the infusion rate based on the desired dose in ng/kg/min.

Body weight [kg]	**Dose [ng/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 a 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 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 ng/kg/min.

The following table 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 body weight on the table, then set the infusion rate based on the desired dose in ng/kg/min.

Body weight [kg]	**Dose [ng/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 for infusion should be prepared every day.

Instructions for handling:

The ampoule contents and diluent must be thoroughly mixed.

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

The contents of 1 ml Iloprost 100 micrograms/ml (i.e. 100 micrograms) is diluted with 500 ml sterile physiological sodium chloride solution or a 5% glucose solution.

The contents of 0.5 ml Iloprost 100 micrograms/ml (i.e. 50 micrograms) is diluted with 250 ml sterile physiological sodium chloride solution or a 5% glucose solution, respectively.

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

The contents of 1 ml Iloprost 100 micrograms/ml (i.e. 100 micrograms) must be diluted with 50 ml sterile physiological sodium chloride solution or 5% glucose solution.

The contents of 0.5 ml Iloprost 100 micrograms/ml (i.e. 50 micrograms) must be diluted with 25 ml sterile physiological sodium chloride solution or 5% glucose solution, respectively.