Package leaflet: Information for the user

Iloprost 10 microgram/ml nebuliser solution

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

What Iloprost is
The active substance of Iloprost 10 microgram/ml nebuliser solution is iloprost. It imitates a natural substance in the body called prostacyclin. Iloprost inhibits unwanted blocking or narrowing of blood vessels and allows more blood to flow through the vessels.

What Iloprost is used for
Iloprost is used to treat moderate cases of primary pulmonary hypertension (PPH) in adult patients. PPH is a category of pulmonary hypertension where the cause of the high blood pressure is not known. This is a condition where blood pressure is too high in the blood vessels between the heart and the lungs.
Iloprost is used to improve exercise capacity (the ability to carry out physical activity) and symptoms.

How Iloprost works
Breathing in the mist carries Iloprost to the lungs, where it can work most effectively in the artery between heart and lungs. Improved blood flow leads to a better supply of oxygen to the body and reduced strain on the heart.

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).
- **if you are at risk of bleeding** – for example, if you have an active ulcer of the stomach or of the first part of the small intestine (duodenal ulcers), if you have suffered a physical injury (trauma), if you are at risk of bleeding within the skull.
- **if you have a heart problem**, such as:
  - Poor blood flow to the heart muscles (severe coronary heart disease or unstable angina). Symptoms can include chest pain.
  - A heart attack within the last six months.
  - A weak heart (decompensated cardiac failure) which is not under close medical observation.
  - Severe unstable heartbeat.
  - A defect of the heart valves (inborn or acquired) that causes the heart to work poorly (not related to pulmonary hypertension).
- **if you have had a stroke within the last 3 months**, or any other occurrence that reduced the blood supply to the brain (e.g. transient ischaemic attack).
- **if your pulmonary hypertension is due to a blocked or narrowed vein** (venous occlusive disease).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Iloprost:
- Inhaling Iloprost might trigger breathing difficulties (see section 4), especially in patients with bronchospasm (sudden constriction of the muscles in the walls of the small airways) and wheezing. Tell your doctor **if you have a lung infection, severe asthma, or chronic lung disease** (chronic obstructive pulmonary disease). Your doctor will monitor you closely.
- **Your blood pressure will be checked before treatment and if it is too low** (less than 85 mmHg for the upper value) then therapy with Iloprost should not be started.
- In general, you will need to **take special care to try and avoid effects of low blood pressure**, such as fainting and dizziness:
  – Tell your doctor if you are taking any other medication because the combined effect with Iloprost may lower your blood pressure further (see below "Other medicines and Iloprost").
  – Stand up slowly when you get out of chairs or bed.
  – If you tend to faint as soon as you get out of bed, it may be helpful to take your first dose of the day while you are still lying down.
  – If you tend to experience fainting episodes, avoid any exceptional straining, for example during physical exertion; it might be useful to inhale Iloprost before. Fainting episodes may be due to the underlying disease. Tell your doctor if they get worse. He/she may consider adjusting your dose or changing your treatment.
- **If you suffer from a weak heart condition such as right heart failure, and feel that your disease is worsening,** tell your doctor. Symptoms can include swelling of feet and ankles, shortness of breath, palpitations, urinating more frequently at night or oedema. Your doctor will consider changing your treatment.
- **If you experience difficulty breathing, cough up blood, and/or sweat excessively these may be signs that you have water in the lungs** (lung oedema)**.** Stop using Iloprost and tell your doctor immediately. He/she will look for the cause and take appropriate measures.
- **If you have liver problems or very severe kidney problems, requiring dialysis,** tell your doctor. You may be gradually introduced to the prescribed dose or be prescribed a lower dose of Iloprost than for other patients (see section 3. "How to use Iloprost").

Contact of Iloprost with skin or swallowing Iloprost
- Do NOT let Iloprost solution come into contact with your skin or eyes. If it does, rinse the skin or your eyes immediately with plenty of water.
- Do NOT drink or swallow Iloprost solution. If you swallow it accidentally, drink plenty of water and tell your doctor.

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 or pharmacist if you are using, have recently used or might use any other medicines. Iloprost and certain 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, such as:
- Beta blockers.
- Nitro-vasodilators.
- ACE inhibitors.

Your blood pressure may drop much further. Your doctor may change the dosage.
- Medicines that thin the blood or inhibit blood clotting, this includes
- Acetylsalicylic acid (ASA - a compound found in many medicines that lower fever and relieve pain).
- Heparin.
- Coumarin-type anticoagulants, such as warfarin or phenprocoumon.

- Non-steroidal anti-inflammatory drugs.
- Non-selective phosphodiesterase inhibitors such as pentoxifylline.
- Selective phosphodiesterase 3 (PDE 3) inhibitors, such as cilostazol or anagrelide.
- Ticlopidine;
- Clopidogrel.
- Glycoprotein IIb/IIIa antagonists, such as:
  - Abciximab.
  - Eptifibatide.
  - Tirofiban.
- Defibrotide.

Your doctor will monitor you carefully.

Before taking any medicine ask your doctor or pharmacist, who has more information on medicines to be careful with or avoid when using Iloprost.

Iloprost with food and drink
Food or drink is not expected to affect Iloprost. However, you should avoid taking food or drink during inhalation.

Pregnancy
- **If you suffer from pulmonary hypertension,** avoid getting pregnant as pregnancy may lead to a worsening of your condition and may even endanger your life.
- **If you could get pregnant,** use reliable contraception from the time you start treatment and during treatment.
- **If you are pregnant, think you may be pregnant or are planning to have a baby,** tell your doctor straight away. Iloprost should only be used during pregnancy if your doctor decides that the potential benefit outweighs the potential risk to you and the foetus.

Breast-feeding
It is not known whether Iloprost passes into human milk. A potential risk to the breast-feeding child cannot be excluded and it is preferable to avoid breast-feeding during iloprost therapy.

Ask your doctor or pharmacist for advice before taking any medicine.

Newborns, infants and pregnant women should not be in the same room while you are inhaling Iloprost.

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.

Iloprost contains ethanol
This medicine contains 0.78 mg of alcohol (ethanol) in each ampoule which is equivalent to 0.81 mg 96% ethanol (v/v). The amount in 1 ml of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicinal product will not have any noticeable effects.

3. How to use Iloprost

Iloprost therapy should only be initiated by a physician experienced in treatment of pulmonary hypertension.

How much to inhale and for how long
Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.
The dose of Iloprost and the duration of treatment that is right for you depend on your individual condition. Your doctor will advise you. Do not change the recommended dose without consulting your doctor first.
Different nebuliser devices can be used to administer Iloprost. Depending on the type of device used and dose prescribed, 1 ml or 2 ml of iloprost are appropriate.

Breelib nebuliser
If you are starting Iloprost treatment or if you switch from an alternative device your first inhalation will be with Iloprost 10 microgram/ml. If you tolerate this dose well, your next dose should be increased using another available presentation on the market containing 20 microgram/ml of iloprost. You should continue on this dose. If you cannot tolerate inhalation of this higher dose talk to your doctor who may decide that you should take Iloprost 10 microgram/ml.

Most people will have 6 to 9 inhalation sessions spread throughout the day. One inhalation session with Breelib will usually last about 3 minutes.
Your doctor will supervise your treatment when you start using the Breelib nebuliser to ensure that you tolerate the dose and speed of inhalation well.

I-Neb AAD nebuliser
In general, when starting Iloprost treatment the first inhaled dose should be 2.5 microgram iloprost as delivered at the mouthpiece. If you tolerate this dose well, your dose should be increased to 5 microgram iloprost and you should continue on this dose. If you are unable to tolerate the 5 microgram dose, the dose should be reduced to 2.5 microgram.

Most people will have 6 to 9 inhalation sessions spread throughout the day. One inhalation session will usually last about 4 to 10 minutes with I-Neb AAD depending on the prescribed dose.

Venta-Neb nebuliser (2 ampoules of Iloprost)
In general, when starting Iloprost treatment the first inhaled dose should be 2.5 microgram iloprost as delivered at the mouthpiece. If you tolerate this dose well, your dose should be increased to 5 microgram and you should continue on this dose. If you are unable to tolerate the 5 microgram dose, the dose should be reduced to 2.5 microgram.

Most people will have 6 to 9 inhalation sessions spread throughout the day. One inhalation session with Venta-Neb will usually last about 4 to 10 minutes depending on the prescribed dose. Depending on your individual needs, Iloprost can be used for long term treatment.

The following information is intended for healthcare professionals only:

Instructions for use and handling

Patients stabilised on one nebuliser should not switch to another nebuliser without close supervision by the treating doctor as different nebulisers have been shown to produce aerosols with slightly different physical characteristics and may have faster delivery of the solution (see section 5.2 of the Summary of Product Characteristics).
To minimise accidental exposure, it is recommended to keep the room well ventilated.

Breelib
When using the Breelib nebuliser please follow the instructions for use provided with the device.
Fill the medication chamber with Iloprost immediately before use.

Device	Drug product	Dose of Iloprost at mouthpiece	Estimated inhalation time
Breelib	Iloprost 10 mcg/ml	2.5 mcg	3 minutes

I-Neb AAD
The I-Neb AAD System is a portable, hand-held, vibrating mesh technology nebuliser system. This system generates droplets by ultrasound, which forces the solution through a mesh. The I-Neb AAD nebuliser has also been shown to be suitable for the administration of iloprost 10 mcg/ml. The measured MMAD of the aerosol droplets was 2.1 micrometres.

This nebuliser monitors the breathing pattern to determine the aerosol pulse time required to deliver the pre-set dose of 2.5 or 5 microgram iloprost.

The dose delivered by the I-Neb AAD system is controlled by the medication chamber in combination with a control disc. Each medication chamber is colour coded and has a corresponding colour coded control disc:
- For the **2.5 microgram** dose the medication chamber with **the red latch is used together with the red control disc**.
- For the **5 microgram** dose the medication chamber with **the purple coloured latch is used together with the purple control disc**.

If you have kidney or liver problems

There is no need to alter the dose in patients with mild or moderate kidney problems (patients with a creatinine clearance >30 ml/min).

If you have very severe kidney problems and require dialysis or if you have liver problems, your doctor will introduce you to Iloprost gradually and possibly prescribe fewer daily inhalations. Start therapy by inhaling 2.5 microgram iloprost using 1 ml ampoule of Iloprost. Use dosing intervals of 3 – 4 hours (this corresponds to a maximum of 6 administrations per day). Thereafter, your doctor may cautiously shorten the dosing intervals depending on how you tolerate the treatment. If your doctor decides to further increase the dose up to 5 microgram, again dosing intervals of 3 - 4 hours should be chosen initially and shortened depending on how you tolerate the treatment.

If you feel that the effect of Iloprost is too strong or too weak, **talk to your doctor or pharmacist**.
Ask your doctor to have someone help you become thoroughly familiar with the use of the nebuliser. You should not switch to another nebuliser without consulting the doctor who is treating you.

How to inhale

For each inhalation session you should use a new ampoule of Iloprost. Just before you start to inhale, break the glass ampoule and pour the solution into the medication chamber following the instructions for use of the nebuliser.

Follow carefully the instructions that come with the nebuliser especially the instructions on hygiene and cleaning of the nebuliser.

Always take Iloprost exactly as your doctor has told you.
- Iloprost nebuliser solution is inhaled using the nebulisers your doctor prescribed (either the Breelib, the Venta-Neb or the I-Neb AAD system).
- The nebuliser turns Iloprost solution into a mist which you breathe in through your mouth.
- For the inhalation you should use a mouthpiece to prevent Iloprost coming into contact with your skin. Do not use a facial mask.
- Follow carefully any instructions that come with the nebuliser. Check with your doctor or pharmacist if you are unsure.
- Any Iloprost solution remaining in the nebuliser after inhalation must be thrown away (see section 5).

Room ventilation
Be sure to ventilate or air the room in which you have taken your Iloprost treatment. Other people might accidentally be exposed to Iloprost through the room air. In particular, newborns, infants and pregnant women should not be in the same room while you are inhaling Iloprost.

Breelib
Fill the medication chamber with Iloprost immediately before use. For filling please follow the instructions for use of the nebuliser.

Device	Drug product	Dose of Iloprost at mouthpiece	Estimated inhalation time
Breelib	Iloprost 10 mcg/ml	2.5 mcg	3 minutes

I-Neb AAD
1. Just before you start to inhale, break the glass ampoule containing 1 ml solution and pour the complete contents into the nebuliser medication chamber.
2. The pre-set dose provided by the I-Neb AAD system is controlled by the medication chamber in combination with a control disc. There are two different colour coded medication chambers. For each medication chamber there is a corresponding colour coded control disc:
- For the **2.5 microgram** dose the medication chamber **with the red coloured latch is used together with the red control disc**.
- For the **5 microgram** dose the medication chamber with **the purple coloured latch is used together with the purple control disc**.
3. In order to ensure that you receive the prescribed dose, check the colour of the medication chamber and the colour of the control disc. They should both have the same colour, either red for the 2.5 microgram dose or purple for the 5 microgram dose.

Device	Dose of Iloprost at mouthpiece	Estimated inhalation time
I-Neb AAD	2.5 microgram 5 microgram	3.2 min 6.5 min

The table below provides a summary of the user instructions of the I-Neb:

Drug products	Dosage	I-Neb AAD	
		Medication chamber latch	Control disc
Iloprost10 mcg/ml	2.5 mcg	red	red
	5 mcg	purple	purple

Venta-Neb
1. Just before you start to inhale, break the glass of 2 ampoules containing 1 ml solution and pour the complete contents into the nebuliser medication chamber.
2. Two programmes can be operated.
3. Your doctor will adjust Venta-Neb to the programme you need to receive the dose prescribed for you.
   - P1 Programme 1: 5 microgram active substance on the mouth piece 25 inhalation cycles.
   - P2 Programme 2: 2.5 microgram active substance on the mouth piece 10 inhalation cycles.
4. You should use the green baffle plate to obtain the optimal droplet size for the administration of Iloprost.

Device	Dose of Iloprost at mouthpiece	Estimated inhalation time
Venta-Neb	2.5 microgram 5 microgram	4 min 8 min

For further details please refer to the instruction manual of the nebuliser device or ask your doctor.

If you use more Iloprost than you should
Using more Iloprost than you should may lead to dizziness, headache, flushing (reddening of the face), nausea (feeling sick), jaw pain or back pain. You may also experience a decrease or an increase in blood pressure, bradycardia (reduced heart rate), tachycardia (increased heart rate), vomiting, diarrhoea or limb pain. If any of these happen when you have used more Iloprost than you should.
- Stop the inhalation session.
- Talk to your doctor.

Your doctor will monitor you and treat any resulting symptoms. A specific antidote is not known.

If you forget to use Iloprost
Do not take a double dose to make up for a forgotten dose. Please ask your doctor what you should do.

If you stop using Iloprost
If you stop or wish to stop treatment, discuss it with your doctor first.

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 following serious side effects may occur. In this case talk to your doctor immediately.

Very common (may affect more than 1 in 10 people):
- Bleeding events (mostly nosebleed (epistaxis) and coughing up blood (haemoptysis)) may very commonly occur, especially if you are also taking blood-thinning medicines (anticoagulants). The risk of bleeding may be increased in patients when inhibitors of platelet aggregation or anticoagulants are given at the same time (see also section 2). Very rarely, fatal cases including bleeding in the brain (cerebral and intracranial haemorrhage) have been reported.

Common (may affect up to 1 in 10 people):
- Fainting (syncope) is a symptom of the illness itself but can also occur during treatment with iloprost (see also section 2 “Warnings and precautions”, for advice on what you can do to avoid this).
- Low blood pressure (hypotension).

Not known (frequency cannot be estimated from the available data):
- Bronchospasm (sudden constriction of the muscles in the walls of the small airways) and wheezing (see also section 2 “Warnings and precautions”).

Below we list other possible side effects by how likely they are:

Very common (may affect more than 1 in 10 people):
- Widening of the blood vessels (vasodilatation). Symptoms can be flushing or reddening of the face.
- Chest discomfort / chest pain.
- Coughing.
- Headache.
- Nausea.
- Pain in jaw/spasm of the jaw muscles (trismus).
- Swelling of the limbs (peripheral oedema).

Common (may affect up to 1 in 10 people):
- Breathing difficulties (dyspnoea).
- Dizziness.
- Vomiting.
- Diarrhoea.
- Pain when swallowing (pharyngolaryngeal irritation).
- Throat irritation.
- Mouth and tongue irritation including pain.
- Rash.
- Fast heartbeat (tachycardia).
- Awareness of fast or hard heartbeat (palpitations).

Not known (frequency cannot be estimated from the available data):
- Reduction in the number of blood platelets (thrombocytopenia).
- Hypersensitivity (i.e. allergy).
- Disturbed sense of taste (dysgeusia).

Other possible effects
- Swelling, mainly of the ankles and legs, due to fluid retention (peripheral oedema) is a very common symptom of the illness itself but can also occur during treatment with Iloprost.

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.

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

This medicine does not require any special storage conditions. Do not freeze.

Any Iloprost solution remaining in the nebuliser after inhalation must be thrown away.

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 with 1 ml contains 10 microgram iloprost (as iloprost trometamol).
- **The other ingredients** are trometamol, ethanol 96%, sodium chloride, hydrochloric acid for pH adjustment, and water for injection.

What Iloprost looks like and contents of the pack

Iloprost is a clear and colourless solution free of visible particles for inhalation with the Breelib, the I-Neb or the Venta-Neb nebuliser.

Iloprost is provided in a clear glass ampoule (hydrolytic class No. I) with identifying colour ring–blue, containing 1.0 ml of solution, packed in blisters in a paper box.

Iloprost is available in packs containing:
10 × 1 ml (2 blisters with 5 ampoules)
30 × 1 ml (6 blisters with 5 ampoules or 5 blisters with 6 ampolues)
40 × 1 ml (8 blisters with 5 ampoules)
42 × 1 ml (8 blisters with 5 ampoules and 1 blister with 2 ampoules or 7 blisters with 6 ampoules)
168 × 1 ml (33 blisters with 5 ampoules and 1 blister with 3 ampoules or 28 blisters with 6 ampoules
Multipacks containing 160 ampoules (4 inner boxes containing 8 blisters with 5 ampoules)
Not all pack sizes may be marketed.

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

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

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For each inhalation session with the I-Neb AAD, the content of one 1 ml ampoule of iloprost is transferred into the medication chamber immediately before use.

Device	Dose of iloprost at mouthpiece	Estimated inhalation time
I-Neb AAD	2.5 microgram 5 microgram	3.2 min 6.5 min

The table below provides a summary of the user instructions of the I-Neb for iloprost:

Drug product	Dosage	I-Neb AAD	
		Medication chamber latch	Control disc
Iloprost 10 mcg/ml	2.5 microgram	red	red
	5 microgram	purple	purple

Venta-Neb
Venta-Neb, a portable ultrasonic battery-powered nebuliser, has also been shown to be suitable for the administration of iloprost 10 mcg/ml. The measured MMAD of the aerosol droplets was 2.6 micrometres. For each inhalation session, the content of two ampoules containing 1 ml of iloprost 10 mcg/ml. nebuliser solution is transferred into the nebuliser medication chamber immediately before use.
Two programmes can be operated:
- P1 Programme 1: 5 microgram active substance on the mouth piece 25 inhalation cycles.
- P2 Programme 2: 2.5 microgram active substance on the mouth piece 10 inhalation cycles.

The selection of the pre-set programme is made by the doctor.

Venta-Neb prompts the patient to inhale by an optical and an acoustic signal. It stops after the pre-set dose has been administered. To obtain the optimal droplet size for the administration of iloprost the green baffle plate should be used. For details refer to the instruction manual of the Venta-Neb nebuliser.

Device	Dose of iloprost at mouthpiece	Estimated inhalation time
Venta-Neb	2.5 microgram 5 microgram	4 min 8 min

The efficacy and tolerability of inhaled iloprost when administered with other nebulising systems, which provide different nebulisation characteristics of iloprost solution, have not been established.