PATIENT PACKAGE LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Ventavis®
Solution for Inhalation

Active ingredient
Each 2 ml ampoule contains:
iloprost 20 micrograms.

Inactive ingredients and allergens: see section 2 "Important information regarding some of the ingredients of the medicine" and section 6 "Further Information".

Read this leaflet carefully in its entirety before using the medicine.
This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
This medicine has been prescribed to treat your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

1) WHAT IS THE MEDICINE INTENDED FOR?

Ventavis is intended to treat patients with moderate to severe primary or secondary pulmonary hypertension caused by a disease in the connective tissue or from use of medicines, or from prolonged pulmonary thrombosis, when surgery is not possible.

Therapeutic group: Ventavis belongs to a group of prostacyclin analog medicines and acts by inhibiting unwanted blockage or narrowing of blood vessels, and thereby improves blood flow in the blood vessels.

How Ventavis works
Inhalation of the mist carries Ventavis directly to the lungs, where it can effectively affect the arteries (blood vessels) between the lungs and heart. Improved blood flow leads to a better supply of oxygen to the body and reduced strain on the heart.

2) BEFORE USING THE MEDICINE

Do not use this medicine if:

- **you are sensitive (allergic)** to iloprost or to any of the other ingredients contained in the medicine. For a list of the inactive ingredients, see section 6 "Further Information".
- you suffer from conditions which may increase the risk of bleeding, such as an active ulcer of the stomach or the duodenum, injuries or risk of bleeding within the skull.
- you suffer from a problem related to the heart, such as:
  - poor blood flow in the blood vessels that nourish the heart muscle (severe coronary heart disease or unstable angina) that can be expressed as chest pain.
  - heart attack within the last six months.
  - a weak heart (decompensated heart failure) that is not under close medical supervision.
  - serious changes in heart rate.
  - a heart valve defect (inborn or acquired) that causes impaired heart function unrelated to your ailment.
- you had a stroke within the last 3 months, or another disruption of blood supply to the brain (e.g., transient ischemic attack).
- your ailment results from narrowing or blockage of the veins (venous occlusive disease).

Special warnings regarding use of this medicine
Before you start using Ventavis, talk to the doctor, pharmacist or nurse.
- Inhaling Ventavis might trigger breathing difficulties (see section 4 "Side Effects"), especially in patients suffering from sudden constriction of the respiratory tract (bronchospasm) and wheezing. Tell the doctor if you have a **lung infection, severe asthma, or chronic obstructive pulmonary disease** (COPD). Your doctor will closely monitor your condition.
- **Your blood pressure should be checked before commencing treatment and if you suffer from low blood pressure** (systolic blood pressure below 85 mmHg), do not start treatment with Ventavis.
- Use of this medicine may cause a reduction in blood pressure. In order to prevent fainting or **other effects of low blood pressure,** such as dizziness, take the following measures:
  - Inform the attending doctor if you are taking other medicines, as their combination with Ventavis may further lower blood pressure (see "Drug interactions" in section 2).
  - Stand up slowly from a sitting or a lying position to standing.
  - If you tend to faint as soon as you get out of bed, it may be helpful to take the first inhalation dose of the day when you wake up, while you are still lying down.
  - If you tend to faint, avoid any exceptional straining, for example during physical exertion; it might be useful for you to inhale Ventavis before physical exertion.
- Fainting may be caused by your ailment. If fainting episodes worsen, inform the attending doctor. There may be a need to readjust the dosage of the medicine or to change the treatment.
- **If you suffer from a heart condition such as a right heart failure, and symptoms that can be suggestive of worsening of the heart condition occur,** such as swelling of feet and ankles, shortness of breath, palpitations, urinating more frequently at night or oedema, refer to the doctor; he may consider changing the treatment.
- **If you suffer from breathing difficulties, bloody cough, and/or excessive sweating, these symptoms may be a sign of water accumulation in the lungs** (pulmonary oedema). Discontinue use of Ventavis and inform the doctor immediately. He will identify the cause and take the appropriate measures.
- **If you are suffering from impaired function of the liver or from a severe impairment in kidney function that requires dialysis,** inform the doctor. You may gradually reach the prescribed dose or the doctor will decide to prescribe a lower dose than that prescribed to other patients (see section 3 "How Should You Use the Medicine?").

Contact of Ventavis with the skin or swallowing Ventavis
- It is important to avoid contact of the Ventavis solution with the skin or eyes. If there is such contact, rinse the skin or eyes immediately with plenty of water.
- Do not drink or swallow the Ventavis solution. If you accidentally swallowed it, drink plenty of water and tell your doctor.

Children and adolescents
The safety and efficacy of the medicine in children and adolescents under 18 years of age have not yet been established.

Drug interactions
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular, if you are taking:
- **medicines to lower blood pressure or to treat heart disease** such as:
  - beta blockers
  - nitro-vasodilators
  - ACE inhibitors

  These medicines can further lower your blood pressure and the doctor may change the dosage.
- **medicines that thin the blood or anticoagulants,** including:
  - aspirin (acetylsalicylic acid), an ingredient found in many preparations to reduce fever and relieve pain
  - heparin
  - coumarin-type anticoagulants such as warfarin or phenprocoumon
  - anti-inflammatory drugs from the NSAID family
  - non-selective phosphodiesterase inhibitors, such as pentoxifylline
  - selective 3 phosphodiesterase (PDE3) inhibitors, such as cilostazol or anagrelide
  - ticlopidine
  - clopidogrel
  - glycoprotein IIb/IIIa inhibitors, such as:
    - abciximab
    - eptifibatide
    - tirofiban
  - defibrotide

The doctor will carefully monitor your condition.

Before taking other medicines, consult the doctor or pharmacist; they have broader knowledge with regard to the medicines you should be cautious with or abstain from when using Ventavis.

Use of the medicine and food
Food or drink are not expected to affect Ventavis. Nevertheless, avoid eating and drinking during inhalation.

Pregnancy, breastfeeding and fertility
Pregnancy
If you suffer from pulmonary hypertension, avoid getting pregnant as pregnancy may lead to worsening of your ailment and may even be life threatening.
If you could become pregnant, use reliable contraceptives from the start of and during treatment.
If you are pregnant, or think you might be pregnant or are planning to become pregnant, tell the doctor immediately. Ventavis can only be used during pregnancy if your doctor decides that the expected benefit outweighs the expected risk to you and your foetus.

Breastfeeding
It is not known whether Ventavis passes into breast milk. A potential risk to a breastfeeding baby cannot be ruled-out; therefore, it is preferable to avoid breastfeeding during treatment with Ventavis.

Fertility
Studies have not shown a negative effect on fertility.
Please consult the doctor or pharmacist before taking any medicine.
Do not inhale Ventavis when new-borns, infants and pregnant women are in the room.

Driving and operating machinery
Use of this medicine may cause a reduction in blood pressure, and, consequently, may cause dizziness in some users; therefore, do not drive or operate machinery if you experience these effects.
Exercise caution during the initiation of treatment until you know what your reactions to the medicine are.

Important information regarding some of the ingredients of the medicine
Ventavis contains a small amount (less than 100 mg per dose) of ethanol (alcohol).

3) HOW SHOULD YOU USE THE MEDICINE?

Always use this medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about your dose or about how to use this medicine.
Treatment with Ventavis will only be initiated by a doctor experienced in treating pulmonary hypertension.

- The dosage and treatment regimen will be determined by the doctor only.

The dose of Ventavis and the duration of treatment that are right for you depend on your medical condition. Your doctor will determine what is appropriate to treat your condition. Do not change the recommended dose without consulting the doctor.

The usual dosage and duration of inhalation are generally:
At initiation of Ventavis treatment, the first inhaled dose should be 2.5 micrograms iloprost (delivered through the mouthpiece of the nebuliser). If you respond well to this dose, the dose will be increased to 5 micrograms and maintained at that dose. If you do not respond well to the 5 micrograms dose, the dose should be reduced to 2.5 micrograms.
Most patients will receive between 6 to 9 inhalations a day, with each inhalation usually lasting for about 4-10 minutes, depending on the prescribed dose and the nebuliser.

In patients suffering from kidney or liver function impairment
There is no need for dose adjustment in patients with mildly to moderately impaired kidney function (patients with a creatinine clearance higher than 30 ml/min).
In patients suffering from severe kidney function impairment and requiring dialysis, or who are suffering from impaired liver function, the doctor will start the treatment with Ventavis gradually and may lower the number of daily inhalations. At initiation of treatment, doses of 2.5 micrograms should be taken at 3-4 hour intervals (corresponding to a maximum of 6 inhalations per day). Thereafter, the doctor may cautiously shorten the intervals between doses, depending on how you tolerate the treatment. If the doctor decides to increase the dose to 5 micrograms, it should, again, be taken at intervals of 3-4 hours, and later, the intervals will be shortened, depending on how you tolerate the treatment.
If you feel that the effect of Ventavis is too weak or too strong, tell your doctor or pharmacist.
Do not exceed the recommended dose.

Treatment duration
Depending on your individual needs, Ventavis can be used for long-term treatment.

- **Inhalation instructions**

Ask your doctor for help in learning how to use the nebuliser. Do not switch nebulisers without first consulting your doctor.
Only use nebulisers designated for this medicine, as determined by the doctor. Various nebulisers have been found suitable for Ventavis administration.

Each time you take a dose, use a new ampoule of Ventavis. Break the ampoule just before use and immediately transfer the solution to the appropriate nebuliser chamber.
Do not use the same ampoule again.

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

Always take Ventavis as determined by the doctor.
- Ventavis is administered through a nebuliser that releases the medicine as a mist that you inhale through the mouth.
- For the inhalation, use a mouthpiece adapted to the mouth and not a mask, to prevent contact with the skin.
- Use as per the instructions that come with the nebuliser package. Consult the doctor or pharmacist if you are uncertain.
- Discard any Ventavis solution remaining in the nebuliser after each inhalation (see section 5 "How should the medicine be stored?").

Room ventilation
- Be sure to ventilate the room in which Ventavis solution was inhaled. Other people may accidentally be exposed to Ventavis through the air in the room. In particular, be sure that new-borns, infants and pregnant women are not in the room while you are inhaling Ventavis.

- **I-Neb AAD nebuliser**

1. Just before you start to inhale, break the glass ampoule containing 2 ml solution, which has two coloured rings (white - pink), 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 the 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 minutes 6.5 minutes

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

The medicine	Ampoule ring colour	Dose	I-Neb AAD nebuliser	
			Medication chamber latch	Control disc
Ventavis 10 microgram/ml	2 ml ampoule with white - pink ring	2.5 microgram	red	red
		5 microgram	purple	purple

If you accidentally inhaled a higher dosage, you may experience dizziness, headache, flushing (reddening of the face), nausea, jaw or back pain.
You may also experience a decrease or an increase in blood pressure, reduced or increased heart rate, vomiting, diarrhoea or limb pains. If any of these effects occur when you have used more Ventavis than you should, stop the inhalations and refer to the doctor. The doctor will monitor your condition and will treat the resulting symptoms. There is no known specific antidote (a substance which counteracts the effect of the medicine).

If you took an overdose or a child has accidentally swallowed some medicine, immediately refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take the medicine, do not take a double dose to compensate for the forgotten dose. Ask the doctor what you should do. Adhere to the treatment regimen recommended by the doctor.

If you stop taking the medicine or wish to stop, consult your doctor before discontinuing use.

Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding the use of the medicine, consult the doctor or pharmacist.

4) SIDE EFFECTS

As with any medicine, use of Ventavis may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of them.

Refer to the doctor immediately if any of the **following serious side effects** occur.

Very common side effects (may affect more than 1 in 10 users):
- Bleeding (mostly nosebleed or coughing up blood) may very commonly occur, primarily in patients also taking anticoagulants. The risk of bleeding may increase in patients concomitantly taking platelet aggregation inhibitors or anticoagulants (see also section 2, "Drug interactions"). Very rarely, fatal cases including bleeding in the brain (cerebral and intracranial haemorrhage) have been reported.

Common side effects (may affect up to 1 in 10 users):
- Fainting may occur as a result of the ailment, but can also occur during treatment with Ventavis (see in section 2 "Special warnings regarding use of this medicine", for instructions on how to avoid this effect).
- Low blood pressure.

Side effects of unknown frequency (frequency cannot be estimated from available data):
- Sudden constriction of the muscles in the walls of the small airways (bronchospasm) and wheezing (see also section 2 "Special warnings regarding use of this medicine").

Additional side effects and their frequencies
Very common side effects (may affect more than 1 in 10 users):
- widening of the blood vessels that can cause flushing or reddening of the face
- chest pain or discomfort
- cough
- headache
- nausea
- pain in the jaw/contraction of the jaw muscles (trismus)
- swelling of the limbs (peripheral oedema)

Common side effects (may affect up to 1 in 10 users):
- breathing difficulties (dyspnoea)
- dizziness
- vomiting
- diarrhoea
- pain when swallowing (pharyngolaryngeal irritation)
- irritation in the throat
- irritation in the mouth and tongue, including pain
- rash
- fast heartbeat (tachycardia)
- sensation of rapid or strong heartbeat (palpitations)

Side effects of unknown frequency (frequency cannot be estimated from the available data):
- reduction in the number of blood platelets (thrombocytopenia)
- hypersensitivity (allergy)
- disturbed sense of taste (dysgeusia)

Other possible effects:
- swelling, mainly of the ankles and legs, due to fluid accumulation, (peripheral oedema) is a very common effect of the ailment, but can also occur during treatment with Ventavis.

If you experience any side effect occurs, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5) HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine must be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package and the ampoule. The expiry date refers to the last day of that month.

Storage conditions
- There are no special storage conditions. Storage at room temperature is recommended.
- Discard the Ventavis solution remaining in the nebuliser at the end of use.
- Do not dispose of medicines in the waste bin or wastewater. Consult a pharmacist as to what to do with medicines you no longer need. This will help protect the environment.

6) FURTHER INFORMATION

- **In addition to the active ingredient, the medicine also contains:** sodium chloride, ethanol 96%, hydrochloric acid 1N, trometamol, water for injection.
- **What the medicine looks like and the contents of the package:** Ventavis is a clear, colourless solution for inhalation in a nebuliser. Ventavis is packaged in transparent ampoules, in packs containing 30 and 90 ampoules of 2 ml. The ampoules are labelled with two coloured rings (pink and white).
- **Registration holder' name and address:** Bayer Israel Ltd., 36 Hacharash St., Hod Hasharon 45240.
- **Manufacturer' name and address:** BerliMed S.A., Madrid, Spain.
- Revised in December 2020 according to MOH guidelines.
- **Registration number of the medicine in the National Drug Registry of the Ministry of Health:** 133 14 31070 00

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