Ventavis 10 microgram/ml nebuliser solution

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1. Name of the medicinal product

Ventavis 10 microgram/ml nebuliser solution

Ventavis 20 microgram/ml nebuliser solution

2. Qualitative and quantitative composition

Ventavis 10 microgram/ml nebuliser solution

1 ml solution contains 10 microgram iloprost (as iloprost trometamol).

Each ampoule with 1 ml solution contains 10 microgram iloprost.

Each ampoule with 2 ml solution contains 20 microgram iloprost.

Ventavis 20 microgram/ml nebuliser solution

1 ml solution contains 20 microgram iloprost (as iloprost trometamol).

Each ampoule with 1 ml solution contains 20 microgram iloprost.

Excipient with known effect:

• Ventavis 10 microgram/ml:

Each ml contains 0.81 mg ethanol 96% (equivalent to 0.75 mg ethanol)

• Ventavis 20 microgram/ml:

Each ml contains 1.62 mg ethanol 96% (equivalent to 1.50 mg ethanol)

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Nebuliser solution.

Ventavis 10 microgram/ml nebuliser solution

Clear, colourless solution.

Ventavis 20 microgram/ml nebuliser solution

Clear, colourless to slightly yellowish solution.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of adult patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.

4.2 Posology and method of administration

Drug product	Suitable inhalation device (nebuliser) to be used		
Ventavis 10 microgram/ml	**Breelib**	**I-Neb AAD**	**Venta-Neb**
Ventavis 20 microgram/ml	**Breelib**	**I-Neb AAD**	

Ventavis should only be initiated and monitored by a physician experienced in the treatment of pulmonary hypertension.

Posology

authorisation

10. Date of revision of the text

At initiation of Ventavis treatment the first inhaled dose should be 2.5 microgram iloprost as delivered at the mouthpiece of the nebuliser. If this dose is well tolerated, dosing should be increased to 5 microgram iloprost and maintained at that dose. In case of poor tolerability of the 5 microgram dose, the dose should be reduced to 2.5 microgram iloprost.

Daily dose

The dose per inhalation session should be administered 6 to 9 times per day according to the individual need and tolerability.

Duration of treatment

The duration of treatment depends on clinical status and is left to the physician's discretion. Should patients deteriorate on this treatment intravenous prostacyclin treatment should be considered.

Special populations

Hepatic impairment

Iloprost elimination is reduced in patients with hepatic dysfunction (see section 5.2).

To avoid undesired accumulation over the day, special caution has to be exercised with these patients during initial dose titration. Initially, doses of 2.5 microgram iloprost should be administered using Ventavis 10 microgram/ml with dosing intervals of 3-4 hours (corresponds to administration of max. 6 times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a dose up to 5 microgram iloprost is indicated, again dosing intervals of 3-4 hours should be chosen initially and shortened according to individual tolerability. An accumulation of iloprost following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

Renal impairment

There is no need for dose adaptation in patients with a creatinine clearance >30 ml/min (as determined from serum creatinine using the Cockroft and Gault formula). Patients with a creatinine clearance of ≤30 ml/min were not investigated in the clinical trials. Data with intravenously administered iloprost indicated that the elimination is reduced in patients with renal failure requiring dialysis. Therefore, the same dosing recommendations as in patients with hepatic impairment (see above) are to be applied.

Paediatric population

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

No data from controlled clinical trials are available.

Method of administration

Ventavis is intended for inhalation use by nebulisation.

To minimize accidental exposure it is recommended to keep the room well ventilated.

The ready-to-use Ventavis nebuliser solution is administered with a suitable inhalation device (nebuliser) (see below and section 6.6).

Patients stabilised on one nebuliser should not switch to another nebuliser without supervision by the treating physician as different nebulisers have been shown to produce aerosols with slightly different physical characteristics and delivery of the solution that may be faster (see section 5.2).

• Breelib

Breelib is a small handheld, battery-powered, breath activated, vibrating mesh technology system.

Ventavis 10 microgram/ml (1 ml ampoule) and Ventavis 20 microgram/ml nebuliser solution

Ventavis 10 microgram/ml nebuliser solution (1 ml ampoule) delivers 2.5 microgram and Ventavis 20 microgram/ml nebuliser solution delivers 5 microgram at the mouthpiece of the Breelib nebuliser.

At initiation of Ventavis treatment or if the patient is switched from an alternative device, the first inhalation should be made with 1 ml ampoule of Ventavis 10 microgram/ml (see section 4.4). If inhalation with Ventavis 10 microgram/ml is well tolerated, the dose should be increased by using Ventavis 20 microgram/ml. This dose should be maintained. In case of poor tolerability of Ventavis 20 microgram/ml, the dose should be reduced by using 1 ml ampoule of Ventavis 10 microgram/ml (see section 4.4).

The duration of an inhalation session with Breelib nebuliser is approximately 3 minutes, which reflects the higher delivery rate of the Breelib compared to other nebulisers.

Patients initiating Ventavis treatment or switching from an alternative device to Breelib should be closely supervised by the treating physician to ensure that dose and speed of inhalation are well tolerated.

When using the Breelib nebuliser please follow the instructions for use provided with the device.

Fill the medication chamber with Ventavis immediately before use.

• 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 been shown to be suitable for the administration of Ventavis 10 microgram/ml (1 ml ampoule) and 20 microgram/ml nebuliser solution. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol measured using I-Neb nebulising systems equipped with power level 10 disc was similar between Ventavis 20 microgram/ml (golden programme) and Ventavis 10 microgram/ml (purple programme) nebuliser solutions (i.e.: around 2 micrometres) but with faster delivery when using Ventavis 20 microgram/ml.

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.

Ventavis 10 microgram/ml nebuliser solution (1 ml ampoule)

should be increased to 5 microgram iloprost using 1 ml ampoule of Ventavis 10 microgram/ml and maintained at that dose. In case of poor tolerability of the 5 microgram dose, the dose should be reduced to 2.5 microgram iloprost.

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.

For the 2.5 microgram dose of Ventavis 10 microgram/ml the medication chamber with the red coloured latch is used together with the red control disc.

For the 5 microgram dose of Ventavis 10 microgram/ml the medication chamber with the purple coloured latch is used together with the purple control disc.

For each inhalation session with the I-Neb AAD, the content of one 1 ml ampoule of Ventavis 10 microgram/ml, with two coloured rings (white - yellow), is transferred into the medication chamber immediately before use.

Drug product	**Ampoule coloured ring**	**Dosage**	**I-Neb AAD**		**Estimated inhalation time**
			Medication chamber latch	**Control disc**	
Ventavis 10 mcg/ml	1 ml ampoule white - yellow ring	2.5 mcg	red	red	3.2 min
		5 mcg	purple	purple	6.5 min

Ventavis 20 microgram/ml nebuliser solution

Only patients who are maintained at the 5 microgram dose and who have repeatedly experienced extended inhalation times with Ventavis 10 microgram/ml, which could result in incomplete inhalation, may be considered suitable for switching to Ventavis 20 microgram/ml.

Close supervision by the treating physician is necessary if switching from Ventavis 10 microgram/ml to Ventavis 20 microgram/ml to control the acute tolerance relating to faster delivery rate of iloprost with the double concentration.

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

For the 5 microgram dose of Ventavis 20 microgram/ml the medication chamber with the gold coloured latch is used together with the gold control disc.

For each inhalation session with the I-Neb AAD, the content of one 1 ml ampoule of Ventavis 20 microgram/ml with two coloured rings (yellow - red), is transferred into the medication chamber immediately before use.

Drug product	**Ampoule coloured rings**	**Dosage**	**I-Neb AAD**	
			Medication chamber latch	**Control disc**
Ventavis 20 mcg/ml	1 ml ampoule yellow - red ring	5 mcg	golden	golden

• Venta-Neb

Venta-Neb, a portable ultrasonic battery-powered nebuliser, has been shown to be suitable for the administration of Ventavis 10 microgram/ml nebuliser solution (2 ml ampoule). The measured MMAD of the aerosol droplets was 2.6 micrometres.

At initiation of Ventavis treatment with Venta-Neb the first inhaled dose should be 2.5 microgram iloprost as delivered at the mouthpiece of the nebuliser using 2 ml ampoule of Ventavis 10 microgram/ml. If this dose is well tolerated, dosing should be increased to 5 microgram iloprost using 2 ml ampoule of Ventavis 10 microgram/ml and maintained at that dose. In case of poor tolerability of the 5 microgram dose, the dose should be reduced to 2.5 microgram iloprost.

For each inhalation session with the Venta-Neb, the content of one 2 ml ampoule of Ventavis 10 microgram/ml with two coloured rings (white – pink) 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 physician.

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 Ventavis 10 microgram/ml nebuliser solution the green baffle plate should be used. For details refer to the instruction manual of the Venta-Neb nebuliser.

Drug product	**Ampoule coloured ring**	**Dose of iloprost at mouthpiece**	**Estimated inhalation time**
Ventavis 10 mcg/ml	2 ml ampoule white - pink ring	2.5 mcg 5 mcg	4 min 8 min

Other nebulising systems

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.

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

- Conditions where the effects of Ventavis on platelets might increase the risk of haemorrhage (e.g. active peptic ulcers, trauma, intracranial haemorrhage).

- Severe coronary heart disease or unstable angina.

- Myocardial infarction within the last six months.

- Decompensated cardiac failure if not under close medical supervision.

- Severe arrhythmias.

- Cerebrovascular events (e.g. transient ischaemic attack, stroke) within the last 3 months.

- Pulmonary hypertension due to venous occlusive disease.

- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

4.4 Special warnings and precautions for use

The use of Ventavis is not recommended in patients with unstable pulmonary hypertension, with advanced right heart failure. In case of deterioration or worsening of right heart failure transfer to other medicinal products should be considered.

Hypotension

Blood pressure should be checked while initiating Ventavis. In patients with low systemic blood pressure and in patients with postural hypotension or receiving medicinal products known to reduce blood pressure levels, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg.

Physicians should be alerted to the presence of concomitant conditions or medicinal products that might increase the risk of hypotension and syncope (see section 4.5).

Syncope

The pulmonary vasodilatory effect of inhaled iloprost is of short duration (one to two hours).

Syncope is a common symptom of the disease itself and can also occur under therapy. Patients who experience syncope in association with pulmonary hypertension should avoid any exceptional straining, for example during physical exertion. Before physical exertion it might be useful to inhale. The increased occurrence of syncope can reflect therapeutic gaps, insufficient effectiveness and/or deterioration of the disease. The need to adapt and/or change the therapy should be considered (see section 4.8).

Patients with diseases of the respiratory tract

Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperactivity (see section 4.8). Moreover, the benefit of Ventavis has not been established in patients with concomitant Chronic Obstructive Pulmonary Disease (COPD) and severe asthma. Patients with concomitant acute pulmonary infections, COPD and severe asthma should be carefully monitored.

Pulmonary veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease. Should signs of pulmonary oedema occur, the possibility of associated pulmonary veno-occlusive disease should be considered and treatment with Ventavis should be discontinued.

Interruption of therapy

In case of interruption of Ventavis therapy, the risk of rebound effect is not formally excluded. Careful monitoring of the patient should be performed, when inhaled iloprost therapy is stopped and an alternative treatment should be considered in critically ill patients.

Renal or hepatic impairment

Data with intravenously administered iloprost indicated that the elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis (see section 5.2). A cautious initial dose titration using dosing intervals of 3-4 hours is recommended (see section 4.2).

Serum glucose levels

Prolonged oral treatment with iloprost clathrate in dogs up to one year was associated with slightly increased fasted serum glucose levels. It cannot be excluded that this is also relevant to humans on prolonged Ventavis therapy.

Undesirable exposure to Ventavis

To minimise accidental exposure, it is recommended to use Ventavis with nebulisers with inhalation-triggered systems (such Breelib or I-Neb), and to keep the room well ventilated.

Newborns, infants and pregnant women should not be subjected to Ventavis in the room air.

Skin and eye contact, oral ingestion

Ventavis nebuliser solution should not come into contact with skin and eyes; oral ingestion of Ventavis solution should be avoided. During nebulisation sessions a facial mask must be avoided and only a mouthpiece should be used.

Ventavis contains ethanol

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

Switching to the Breelib nebuliser

Limited data are available on the use of the Breelib nebuliser. For patients being switched from an alternative device to the Breelib nebuliser the first inhalation should be made with Ventavis 10 microgram/ml (1ml ampoule) delivering 2.5 microgram iloprost at the mouthpiece and under close medical supervision to ensure that the faster inhalation provided by Breelib is

inhaled with an alternative device (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

Iloprost may increase the effects of vasodilatators and antihypertensive agents and then favour the risk of hypotension (see section 4.4). Caution is recommended in case of co-administration of Ventavis with other antihypertensive or vasodilatating agents as dose adjustment might be required.

Since iloprost inhibits platelet function its use with the following substances may enhance iloprost-mediated platelet inhibition, thereby increasing the risk of bleeding:

• anticoagulants such as

- heparin,

- oral anticoagulants (either coumarin-type or direct)

• or other inhibitors of platelet aggregation, such as

- acetylsalicylic acid,

- non-steroidal anti-inflammatory medicinal products,

- non-selective phosphodiesterase inhibitors like pentoxifylline,

- selective phosphodiesterase 3 (PDE3) inhibitors like cilostazol or anagrelide

- ticlopidine,

- clopidogrel,

- glycoprotein IIb/IIIa antagonists, like:

o abciximab,

o eptifibatide

o tirofiban

o defibrotide.

A careful monitoring of the patients taking anticoagulants or other inhibitors of platelet aggregation according to common medical practice is recommended.

Intravenous infusion of iloprost has no effect either on the pharmacokinetics of multiple oral doses of digoxin or on the pharmacokinetics of co-administered tissue plasminogen activator (t-PA) in patients.

Although, clinical studies have not been conducted, *in vitro* studies investigating the inhibitory potential of iloprost on the activity of cytochrome P450 enzymes revealed that no relevant inhibition of drug metabolism via these enzymes by iloprost is to be expected.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies have shown reproductive effects (see section 5.3).

There is a limited amount of data from the use of iloprost in pregnant women. Taking into account the potential maternal benefit, the use of Ventavis during pregnancy may be considered in those women who choose to continue their pregnancy, despite the known risks of pulmonary hypertension during pregnancy.

Breast-feeding

It is not known whether iloprost/metabolites are excreted in human breast milk. Very low levels of iloprost into milk were observed in rats (see section 5.3). A potential risk to the breast-feeding child cannot be excluded and it is preferable to avoid breast-feeding during Ventavis therapy.

Fertility

Animal studies have not shown harmful effect of iloprost on fertility.

4.7 Effects on ability to drive and use machines

Ventavis has major influence on the ability to drive and use machines for patients experiencing hypotensive symptoms such as dizziness.

Care should be exercised during initiation of therapy until any effects on the individual have been determined.

4.8 Undesirable effects

Summary of the safety profile

In addition to local effects resulting from administration of iloprost by inhalation such as cough, adverse reactions with iloprost are related to the pharmacological properties of prostacyclins.

The most frequently observed adverse reactions (≥ 20 %) in clinical trials include vasodilatation (including hypotension), headache and cough. The most serious adverse reactions were hypotension, bleeding events, and bronchospasm.

Tabulated list of adverse reactions

The adverse reactions reported below are based on pooled clinical trial data from phase II and III clinical trials involving 131 patients taking the medicinal product and on data from post-marketing surveillance. The frequencies of adverse reactions are defined as very common (≥1/10) and common (≥1/100 to <1/10). The adverse reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated from clinical trial data, are listed under "Frequency

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