Ventavis 10 mcg/ml

Solution For Inhalation

1. NAME OF THE MEDICINAL PRODUCT

Ventavis 10 micrograms/mL Solution For Inhalation

2. QUANTITATIVE AND QUALITATIVE COMPOSITION

1 mL nebuliser solution contains 10 micrograms iloprost (as iloprost trometamol).
One ampoule with 2 mL nebuliser solution contains 20 micrograms iloprost (as iloprost trometamol).

3. PHARMACEUTICAL FORM

Nebuliser solution

4. CLINICAL PARTICULARS

4.1 Indications

Treatment of moderate or severe stages of

- Idiopathic pulmonary arterial hypertension [IPAH] and familial pulmonary arterial hypertension [FPAH]
- Pulmonary arterial hypertension [APAH] associated with connective tissue disease, and pulmonary arterial hypertension associated with drugs or toxins
- Pulmonary hypertension due to chronic thrombotic and/or embolic disease where surgery is not possible

4.2 Dosage and method of administration

4.2.1 Method of administration

The ready-to-use Ventavis 10 microgram / mL nebuliser solution is administered with a suitable inhalation device (nebuliser) as recommended in the section “Instructions for use / handling”.

Previous therapy should be adjusted to individual needs (see section “Interaction with other medicinal products and other forms of interaction”).

4.2.2 Dosage regimen

Adults

At initiation of Ventavis 10 microgram / mL treatment the first inhaled dose should be 2.5 microgram iloprost (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 microgram and maintained at that dose. In case of poor tolerability of the 5.0 microgram dose, the dose should be reduced to 2.5 microgram.

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

Depending on the desired dose at the mouthpiece and on the nebuliser, the duration of an inhalation session is approximately 4 to 10 minutes.

Duration of treatment

Long term 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.

4.2.3 Additional information on special populations

Patients with hepatic impairment
Iloprost elimination is reduced in patients with hepatic dysfunction (see section "Pharmacokinetic Properties").

Caution should be used during therapy in patients with Child-Pugh class B or more severe hepatic impairment. It should also be used with caution in patients with mild to moderate hepatic impairment. 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 micrograms should be administered 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 further increase in the dose up to 5.0 micrograms 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.

Patients with 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 with Ventavis. Based on data with intravenously administered iloprost the elimination is reduced in patients with renal failure requiring dialysis. For dosing recommendations, see "Patients with hepatic impairment".

Children and adolescents (below 18 years of age)
Currently only sporadic reports of use in children and adolescents are available. Until further data become available. Ventavis should not be used in patients below 18 years of age (see section, "Special warnings and precautions for use").

4.3 Contraindications

- Pregnancy
- Lactation
- Conditions where the effects of Ventavis on platelets might increase the risk of hemorrhage (e.g. active peptic ulcers, trauma, intracranial hemorrhage)
- 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
- Suspected pulmonary congestion
- Cerebrovascular events [e.g. transient ischemic 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
- Hypersensitivity to iloprost or to any of the excipients

4.4 Special warnings and precautions for use

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

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.

4.4.1 Risk of syncope

Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope (see section “Interaction with other medicinal products and other forms of interaction”).

Syncope is also a common symptom of the disease itself. 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. If syncope occurs on rising, it may be useful to take the first dose of the day on waking, while still recumbent. The pulmonary vasodilatory effect of inhaled iloprost is of short duration (one to two hours).The increased occurrence of syncopes can reflect therapeutic gaps and/or deterioration of the disease. The need to adapt and/or change the therapy should be considered (see section “Undesirable effects”).

4.4.2 Hypotension

Vital Signs should be monitored while initiating Ventavis. In Patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mm Hg.

4.4.3 Bronchospasm

Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperreactivity (see section “Undesirable effects”). 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.

4.4.4 Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Ventavis should not be used as the first treatment option in thromboembolic pulmonary hypertension if surgery is feasible.

4.4.5 Pulmonary veno-occlusive disease (PVOD)

Should signs of pulmonary edema occur when inhaled iloprost is administered in patients with pulmonary hypertension, the possibility of associated pulmonary veno-occlusive disease should be considered. The treatment should be stopped.

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.

4.4.6 Patients with hepatic and renal impairment

Iloprost elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis (see section “Pharmacokinetic Properties”). A cautious initial dose titration using dosing intervals of 3 – 4 hours is recommended (see section “Dosage and method of Administration”).

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 man on prolonged Ventavis therapy.

4.4.7 Pregnancy and lactation

There are insufficient data from the use of Ventavis in pregnant women. Therefore, women of child bearing potential should use effective contraceptive measures during treatment with Ventavis.

It is not known whether iloprost/metabolites are excreted in human milk. Therefore women should not breast-feed during treatment with Ventavis (see section ‘Pregnancy and lactation’).

4.5 Interaction with other medicinal products and other forms of interaction

Iloprost may increase the antihypertensive effect of vasodilating and antihypertensive agents (see section,”Special warnings and precautions for use”.). Caution is recommended in case of co-administration of Ventavis with vasodilating or antihypertensive agents as dose adjustment might be required.
Because iloprost inhibits platelet function, its use with anticoagulants (such as heparin, coumarin-type anticoagulants), or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, non-selective phosphodiesterase inhibitors, selective phosphodiesterase 3 (PDE3) inhibitors and nitro vasodilators) may enhance Iloprost-mediated platelet inhibition, thereby increasing the risk of bleeding(see section ‘Undesirable effects’). A careful monitoring of the patients taking anticoagulants or other inhibitors of platelet aggregation according to common medical practice is recommended.
Oral premedication with acetylsalicylic acid up to 300 mg per day over a period of 8 days had no impact on the pharmacokinetics of iloprost.

In an animal study, it was found that iloprost may result in a reduction in tissue-type plasminogen activator (t-PA) steady-state plasma concentration. The results of human studies show that iloprost infusions do not affect the pharmacokinetics of multiple oral doses of digoxin in patients and iloprost has no impact on the pharmacokinetics of co-administered t-PA.

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 have to be expected.

In animal experiments, the vasodilatory effect of iloprost is attenuated when the animals are pretreated with glucocorticoids, while the inhibitory effect on platelet aggregation remains unaffected. The significance of this finding for use of Ventavis in man is not known.

4.6 Pregnancy and Lactation

Iloprost must not be administered to pregnant or lactating women.

4.6.1 Pregnancy Women with pulmonary hypertension (PH) must avoid pregnancy as it may lead to life-threatening exacerbation of the disease.

There are insufficient data from the use of Ventavis in pregnant women. Studies in rats with continuous intravenous iloprost administration have shown digit anomalies in a few fetuses/pups without dose dependence. These effects are not regarded as teratogenic but are most likely related to iloprost-induced growth retardation due to hemodynamic alterations in the fetoplacental unit and have not been observed in other species (see section “Preclinical safety data”). The potential risk for humans is unknown.
Therefore, women of child-bearing potential should use effective contraceptive measures during treatment with Ventavis.

4.6.2 Lactation
It is not known whether iloprost/metabolites are excreted in human milk. Low levels of iloprost or its metabolites are excreted into milk by lactating rats.Therefore women should not breast-feed during treatment with Ventavis (see section ‘Contraindications’ and ‘Special warnings and precautions for use’).

4.7 Effects on ability to drive or use machines

Care should be exercised during initiation of therapy until any effects on the individual have been determined. In patients experiencing hypotensive symptoms such as dizziness, ability to drive or operate machines may be seriously affected.

4.8 Undesirable Effects

Summary of the safety profile

In addition to local effects resulting from administration of iloprost by inhalation such as increased cough, adverse reactions with iloprost are related to the pharmacological properties of prostaglandins. The most frequently observed adverse reactions (≥ 20%) in clinical trials

include vasodilatation, headache and cough. The most serious adverse reactions were hypotension, bleeding events and bronchospasm.

Tabulated list of adverse reactions

The adverse drug reactions observed with Ventavis are represented in the table below. They are classified according to System Organ Class. The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The adverse drug reactions (ADRs) reported below are based on pooled clinical trial data from phase II and III clinical trials involving 131 patients taking Ventavis 10 microgram / ml and on data from post-marketing surveillance,

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention: very common: ≥1/10 and common: ≥1/100 to < 1/10.

The ADRs identified only during post marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions reported in patients treated with Ventavis

System Organ Class (MedDRA)	Very common	Common	Not known
Blood and lymphatic system disorders	Bleeding events*§		Thrombocytopenia
Immune system disorders			Hypersensitivity
Nervous system disorders	Headache	Dizziness	
Cardiac disorders		Tachycardia Palpitations	
Vascular disorders	Vasodilation	Hypotension* Syncope§	
Respiratory, thoracic and mediastinal disorders	Chest pain Cough	Dyspnea Pharyngolaryngeal pain Throat irritations	Bronchospasm* / Wheezing Nasal congestion
Gastrointestinal disorders	Nausea	Diarrhea Vomiting Mouth and tongue irritation including pain	Dysgeusia
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal, connective tissue and bone disorders	Pain in jaw/trismus	Back pain	
General disorders and administration site conditions	Peripheral edema§		

* life-threatening and/or fatal cases have been reported

§ see section ‘Description of selected adverse reaction’

Description of selected adverse reactions

Bleeding events (mostly epistaxis and hemoptysis) were very common as expected in this patient population with a high proportion of patients taking anticoagulant comedication. The risk of bleeding may be increased in patients when inhibitors of platelet aggregation or anticoagulants are given concomitantly (see section ‘Interaction with other medicinal products and other forms of interaction’). Fatal cases of cerebral and intracranial hemorrhage have been reported.

In clinical trials peripheral edema was reported in 12.2% of patients on iloprost and 16.2 % of patients on placebo. Peripheral edema is a very common symptom of the disease itself, but it may also be related to the therapy.

Syncope is a common symptom of the disease itself, but can also occur under therapy. The increased occurrence of syncopes can be related to the deterioration of the disease or insufficient effectiveness of the product.

Adverse reactions in healthy volunteers
In a 4-arm equally randomized placebo-controlled study in 160 healthy volunteers, inhaled doses of iloprost solution were given either with a fixed dose of 2.5 microgram iloprost 6 times daily (total daily dose of 15 microgram), or beginning with 5.0 microgram and increasing up to 20 microgram, or the highest tolerated dose for a total of 6 dose inhalations (total cumulative dose of 70 microgram).

In the fixed dose group of 2.5 microgram per inhalation chest pain, discomfort (32.5 %), pharyngolaryngeal pain, throat irritation (22.5 %) and nausea (7.5 %) – all non-serious and mild in intensity – occurred more frequently in comparison with the adverse reactions obtained from the placebo-controlled phase II and III studies in patients with doses of 2.5 microgram or 5 microgram per inhalation.

Five patients were unable to increase the dose up to 20 microgram per inhalation because of mild to moderate transient chest pain, discomfort, usually accompanied by headache, dizziness and nausea.

4.9 Overdose

4.9.1 Symptoms

Cases of overdose were reported. Frequently observed symptoms following overdose are dizziness, headache, flushing, nausea, jaw pain or back pain. Hypotension, an increase of blood pressure, bradycardia or tachycardia, vomiting, diarrhea and limb pain might also be possible.

4.9.2 Therapy
A specific antidote is not known. Interruption of the iloprost administration, monitoring and symptomatic measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Iloprost, the active ingredient of Ventavis, is a synthetic prostacyclin analogue.
The pharmacological effects after inhalation of Ventavis are:
Direct vasodilatation of the pulmonary arterial bed occurred with consecutive significant improvement of pulmonary artery pressure, pulmonary vascular resistance and cardiac output as well as mixed venous oxygen saturation. Effects on systemic vascular resistance and systemic arterial pressure were minor.

Clinical Trials
Clinical studies on the efficacy and safety of Ventavis solution for inhalation have been conducted. A phase II study (AOO794) and a phase III study (AO2997) comprise the main efficacy and safety data.

Phase II Study (AOO794)
This was an open-label randomised phase II multicentre study which included a three month controlled phase (with either inhaled iloprost added to conventional therapy or conventional therapy alone) before patients went on to an open-label, long term therapy with inhaled iloprost for up to two years. Patients with NYHA functional class II, III or IV were included with a mPAP of about 30 or 40 mmHg, for PPH or SPH respectively. 30 patients were randomised to the iloprost group and 33 to the control group. Fifteen patients prematurely discontinued study medication (eight iloprost and seven control patients). After the end of the three month phase, 52 patients entered the long-term treatment phase with inhaled iloprost for up to 24 months. During the randomised phase the median nominal daily iloprost dose was 100µg (50µg -150µg). During the long term study phase the median range daily dose was 100µg (range 50µg to 200µg).

The following results were obtained during the three month randomised phase:
• Improvement in the physical condition of the patients receiving iloprost (all health related quality of life outcomes showed more frequent improvement with iloprost).
• Significant improvement with iloprost in patients who improved by at least one NYHA class at month two (p=0.013), improvement of the Mahler focal score at month two and the Mahler transition score at each time point.
• Non significant improvement in walking distance with iloprost (p=0.620)
• Mortality was similar in both treatment groups.
• Statistically significant difference between treatment groups in favour of iloprost. At month 3, p = 0.046.

The following interim results were obtained from 9-12 months of the follow up phase:
• Patients remained stable or improved (NYHA class and Mahler dyspnea index).
• Pre inhalation values of haemodynamics and gas exchange remained stable compared to baseline.
• Peak haemodynamic effect improved significantly.
• Acute response to iloprost inhalation maintained after long term treatment. No development of drug effect tolerance.

Phase III Study (AO2997)
This was a multicentre double-blind randomized placebo-controlled efficacy and safety study of

12 weeks duration. The study included 203 patients belonging to class III or IV NYHA functional class. The median inhaled iloprost daily dose was 30µg divided into 6 inhalations (range 12.5µg to 45µg). There was no tolerance development.

The primary end point was a combined responder criterion consisting of improvement in exercise capacity at 12 weeks by at least 10% versus baseline and improvement by at least one NYHA class at 12 weeks via baseline and no deterioration of PHT or death at any time before 12 weeks.

Iloprost showed superior efficacy compared to placebo with 16.8% (17/101). Iloprost patients meeting the combined responder end point while only 4.9% (5/102) of placebo patients reached the primary end point (p = 0.007).

Exercise capacity: at week 12, at least 10% increase in the six minute walking distance as compared to baseline was noted in 37.6% of the iloprost group and 25.5% of the control group (p = 0.059).

NYHA functional class: in the iloprost group 24.8% improved versus 12.7% in the placebo group (p = 0.032).

Death and defined criteria of deterioration: One patient in the iloprost group and 4 patients in the placebo group died (p=0.369) during the 12 week observation period. One iloprost patient died after having reached premature end of study.

During the follow up period (up to week 16), 2 further patients originally randomised to the iloprost group and 3 placebo patients died.

There was no statistically significant difference in the rate of death or deterioration in patients taking iloprost compared to placebo.

Mahler dyspnea index: iloprost showed a significantly better improvement compared to placebo (p = 0.015).

The overall incidence of side effects reported up to 12 weeks were comparable between the treatment groups for both the Phase I and Phase II Study.
The HaloLite nebuliser system was used to administer Ventavis in the clinical trial.

Overview of secondary endpoints

		Iloprost N=101	**Placebo N=102**	**Treatment Effect p-value**
Improvement in NYHA class**	n(%)	25 (24.8%)	13 (12.7%)	0.032 [4)]
Improvement of WD of 10% vs baseline** Walking distance- Change from baseline *# (m)mean > SD median change	n(%)	38(37.6%) n = 95 22.2 ± 71.4 20.0	26 (25.5%) n = 85 -3.3 ± 74.2 0.0	NS [7)] 0.032 [1)]

Perceived exertion (RPE) Scale*# Absolute change to baseline Mean, SD		n = 95 -0.38 ± 2.7	n = 85 0.04 ± 2.9	NS [7]
Deterioration Mortality until week 12	n(%) n(%)	5(4.9%) 1(1.0%)	9 (8.8%) 4 (3.9%)	NS [7] NS [7]
Need for transplantation* Patients newly scheduled	n(%)	2(2.0%)	4 (3.9%)	NS [7]
MDI focal score – change To baseline * Mean > SD		n = 96 0.448 ±1.691	n = 86 0.174 ±1.365	NS [7]
MDI transition score* Mean > SD		n = 96 1.42 ± 2.6	n = 86 0.30 ± 2.5	0.015 [7]
EQ-VAS-change to Baseline* Mean > SD		N = 95 5.43 ± 17.32	N = 82 -1.77 ±18.95	0.016[5]

* Findings based on observed cases only.
** Component of the primary endpoint.
# Values obtained at week 12 after inhalation.
1) Non-parametric analysis of covariance with baseline value as covariate.
2) Two-sided Kruskal-Wallis test on absolute values.
3) Fisher's exact test.
4) Stratified Mantel-Haenszel test.
5) Analysis of covariance.
6) One-way ANOVA model.
7) NS = not significant

5.2 Pharmacokinetic properties

Absorption
When iloprost is administered via inhalation in patients with pulmonary hypertension or healthy volunteers (iloprost dose at the mouthpiece: 5 microgram : inhalation time between 4.6 – 10.6 min), mean peak concentrations of about 100 to 200 picograms/mL were observed at the end of inhalation. These concentrations decline with half-lives between approximately 5 and 25 minutes. Within 30 minutes to 2 hours after the end of inhalation, iloprost is not detectable in the central compartment (limit of quantification 25 picograms/mL).

Distribution
No studies performed following inhalation. Following intravenous infusion, the apparent steady-state volume of distribution was 0.6 to 0.8 L/kg in healthy subjects. Total plasma binding of iloprost is concentration independent in the range of 30 to 3000 picograms/mL and amounts to approximately 60 %, of which 75% is due to albumin binding.

Metabolism
No studies to investigate the metabolism of iloprost were performed following inhalation of Ventavis.In vitro studies suggest, however, that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation. After intravenous administration, iloprost is

extensively metabolized via β-oxidation of the carboxyl side chain. No unchanged substance is eliminated. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form in 4 diastereoisomers. Tetranor-iloprost is pharmacologically inactive as shown in animal experiments.

In vitro studies revealed that cytochrome P450-dependent metabolism plays only a minor role in the biotransformation of iloprost.

Elimination
No studies performed following inhalation. In subjects with normal renal and hepatic function, the disposition of iloprost following intravenous infusion is characterized in most cases by a two-phase profile with mean half-lives of 3 to 5 minutes and 15 to 30 minutes. The total clearance of iloprost is about 20 mL/kg/min which indicates extrahepatic contribution to the metabolism of iloprost. A mass-balance study was done using ^{3}H-iloprost in healthy subjects. Following intravenous infusion, the recovery of total radioactivity is 81 %, and the respective recoveries in urine and faeces are 68 % and 12 %. The metabolites are eliminated from plasma and with urine in 2 phases, for which half-lives of about 2 and 5 hours (plasma) and 2 and 18 hours (urine) have been calculated.

Characteristics in specific patient groups
Renal dysfunction:
In a study with intravenous infusion of iloprost, patients with end stage renal failure undergoing intermittent dialysis treatment are shown to have a significantly lower clearance (mean CL = 5±2 mL/minute/kg) than that observed in patients with renal failure not undergoing intermittent dialysis treatment (mean CL = 18 ± 2 mL/minute/kg).

Hepatic dysfunction:
Because iloprost is extensively metabolized by the liver, the plasma levels of the drug are influenced by changes in hepatic function. In an intravenous study, results were obtained involving 8 patients suffering from liver cirrhosis. The mean clearance of iloprost is estimated to be 10 mL/minute/kg. The results indicate that clearance of iloprost was reduced by 50% in the group of cirrhotic patients compared to the historical control patients.

Age and gender:
Gender is not of clinical relevance to pharmacokinetics of Iloprost. Pharmacokinetics in elderly patients have not been investigated.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use

Reproduction toxicology

In embryo- and fetotoxicity studies in rats continuous intravenous administration of iloprost led to anomalies of single phalanges of the forepaws in a few fetuses/pups without dose dependence.

These alterations are not considered as true teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to hemodynamic alterations in the

fetoplacental unit. It can be assumed that this growth retardation is widely reversible and can be compensated during the postnatal development. In comparable embryotoxicity studies in rabbits and monkeys no such digit anomalies or other gross-structural abnormalities were observed even after considerably higher dose levels which exceeded the human dose multiple times.

In rats a passage of extremely low levels of iloprost into the milk was observed.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Trometamol
Ethanol
Sodium chloride
Hydrochloric acid
Water for injections

Storage Conditions
Store below 30°C.

Shelf Life
Please refer to labels

Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Instructions for use/handling
For each inhalation session a new ampoule of Ventavis should be used. The content of the ampoule has to be completely transferred into the nebuliser chamber immediately before use. Nebuliser solution not used in one inhalation session has to be discarded. In addition, instructions for hygiene and cleaning of the nebulizers provided by the device manufacturers should be followed carefully.

Two compressed air nebuliser systems, HaloLite and Prodose, have been shown to be suitable nebulisers for the administration of Ventavis 10 microgram / mL. For each inhalation session the content of one ampoule containing 2 ml of Ventavis nebuliser solution will be transferred into the nebuliser medication chamber immediately before use. HaloLite and Prodose are dosimetric systems. They stop automatically after the pre-set dose has been delivered. The inhalation time depends on the patient’s breathing pattern.

Device	**Dose of iloprost at mouthpiece**	**Estimated Inhalation time (frequency of 15 breaths per minute)**
HaloLite	2.5 micrograms 5 micrograms	4 to 5 min 8 to 10 min
Prodose	2.5 micrograms 5 micrograms	4 to 5 min 8 to 10 min

For a dose of 5 micrograms iloprost at mouthpiece it is recommended to complete two inhalation cycles with 2.5 micrograms pre-set dose program with a filling of one ampoule containing 2 ml Ventavis nebuliser solution, which shows two coloured rings (white – pink).

For details refer to the instruction manuals of the HaloLite and Prodose nebuliser.

VentaNeb, a portable ultrasonic battery-powered nebuliser, has also been shown to be suitable for the administration of Ventavis. The measured MMAD of the aerosol droplets was 2.6 micrometres. For each inhalation session, the content of one ampoule containing 2 ml of Ventavis nebuliser solution and showing two coloured rings (white – pink) will be transferred into the nebuliser medication chamber immediately before use.

Two programs can be operated:

P1 Program 1: 5.0 micrograms active substance on the mouth piece 25 inhalation cycles.

P2 Program 2: 2.5 micrograms active substance on the mouth piece 10 inhalation cycles.

The selection of the pre-set program is made by the physician.

Device	**Dose of iloprost at mouthpiece**	**Estimated Inhalation time**
VentaNeb	2.5 micrograms 5 micrograms	4 min 8 min

VentaNeb 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 the green baffle plate should be used. For details refer to the instruction manual of the VentaNeb nebuliser.

The I-Neb AAD System is a portable, hand-held, vibrating mesh technology nebuliser system, This system generates droplets by ultrasound, which is forcing the solution through a mesh. The I-Neb AAD nebuliser has also been shown to be suitable for the administration of Ventavis. 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 micrograms iloprost.

The pre-set dose provided by the I-Neb AAD system is controlled by the medication chamber and 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 micrograms dose the medication chamber (350 microliter) with the red latch is used together with the red control disc.

For the 5 micrograms dose the medication chamber (650 microliter) 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 nebulizer solution, showing two coloured rings (White-Yellow), will be transferred into the appropriate nebulizer medication chamber immediately before use.

Device	**Dose of iloprost at mouthpiece**	**Estimated Inhalation time**
I-Neb AAD	2.5 micrograms 5 micrograms	3.2 min 6.5 min

Since the I-Neb nebuliser has been shown to produce an aerosol with slightly different physical characteristics to those of HaloLite, Prodose and VentaNeb devices and a faster delivery of the solution, patients stabilised on one nebuliser should not switch to another nebuliser without supervision by the treating physician.

To minimize accidental exposure, it is recommended to use Ventavis with nebulisers with a filter or inhalation-triggered systems, and to keep the room well ventilated.

Presentation
Ampoules of 3 ml, colorless, glass type I, containing 2 ml nebuliser solution,
Packs containing 30 ampoules.

Manufacturer
Berlimed SA
Poligono Industrial Santa
Rosa S/N Alcala De Henares
Madrid
Spain

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