**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Ventavis 10 microgram/ml nebuliser solution.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml solution contains 10 micrograms iloprost (as iloprost trometamol). Each 2-ml ampoule contains 20 micrograms iloprost (as iloprost trometamol).

For excipients, see 6.1.

## 3. PHARMACEUTICAL FORM

Nebuliser solution.
Clear, colourless solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 4.2 Posology and method of administration

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

Ventavis is intended for inhalation use by nebulisation.

Adults

- Dose per inhalation session:

The recommended dose is 2.5 micrograms or 5.0 micrograms of inhaled iloprost (as delivered at the mouthpiece of the nebuliser) according to the individual need and tolerability.

Two compressed air nebuliser systems, HaloLite and Prodose, have been shown to be suitable nebulisers for the administration of Ventavis. With both systems the mass median aerodynamic diameter of the aerosol droplet (MMAD) with iloprost was between 2.6 and 2.7 µm. For each inhalation session the content of one 2-ml ampoule of Ventavis 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 µg<br>5 µg | 4 to 5 min<br>8 to 10 min |
| Prodose | 2.5 µg<br>5 µg | 4 to 5 min<br>8 to 10 min |

For a dose of 5 µg iloprost at mouthpiece it is recommended to complete two inhalation cycles with 2.5 µg pre-set dose program with a filling of one 2-ml ampoule.

In addition Venta-Neb, a portable ultrasonic battery-powered nebuliser, has been shown to be suitable for the administration of Ventavis. The measured MMAD of the aerosol droplets was 2.6 µm. For each inhalation session, the content of one 2-ml ampoule of Ventavis will be transferred into the nebuliser medication chamber immediately before use.

Two programs can be operated:
PI Program 1 : 5,0 µg active substance on the mouth piece 25 inhalation cycles.
P2 Program 2 : 2,5 µg active substance on the mouth piece 10 inhalation cycles.
The selection of the pre set program 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 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 µg<br>5 µg | 4 min<br>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.

- 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.

Patients with 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 µg should be administered with dosing intervals of at least 3 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 µg is indicated, again dosing intervals of at least 3 hours should be chosen initially and shortened according to individual tolerability. A further undesired accumulation of the medicinal product 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.

Children and adolescents (below 18 years of age)

Currently no experience in children and adolescents is available.

## 4.3 Contraindications

Hypersensitivity to iloprost or to any of the excipients.

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.

Pregnancy, lactation.

## 4.4 Special warnings and special 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.

The pulmonary vasodilatory effect of inhaled iloprost is of short duration (one to two hours). 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 occurrence of a nocturnal or exertional syncope reflects therapeutic gaps and/or insufficient efficiency, and the need to adapt and/or change the therapy should be considered (see section 4.8).

The benefit of Ventavis has not been established in patients with chronic pulmonary bronchitis and severe asthma. Patients with acute pulmonary infections should be carefully monitored.

In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic arterial hypotension less than 85 mmHg.

Should signs of pulmonary oedema 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.

Iloprost 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 at least 3 hours is recommended (see section 4.2).

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.

To minimise accidental exposure, it is recommended to use Ventavis with nebulisers with inhalation-triggered systems (HaloLite/Prodose), and to keep the room well ventilated.

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.

**4.5 Interaction with other medicinal products and other forms of interaction**

Iloprost may increase the effect of vasodilatators and antihypertensive agents.

Iloprost can inhibit platelet function and 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, ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists: abciximab, eptifibatide and tirofiban) may increase the risk of bleeding. A careful monitoring of the patients taking anticoagulants according to common medical practice is recommended. The concomitant use of other platelet inhibitors should be avoided in patients taking anticoagulants.

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 have to be expected.

**4.6 Pregnancy and lactation**

- Pregnancy

There are no adequate data from the use of Ventavis in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Ventavis is contra-indicated during pregnancy. Women of child-bearing potential should use effective contraceptive measures during treatment.

- Lactation

It is not known whether Ventavis enters the breast milk. The medicinal product must not be administered to breast feeding mothers (see section 4.3).

**4.7 Effects on ability to drive and 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, the abilityto drive or operate machines may be affected.

**4.8 Undesirable effects**

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 prostacyclins.

The frequencies of the adverse reactions reported below (very common >10%, common >1 - 10%) are based on clinical trial data.

**Cardiovascular disorders**

Very common: vasodilatation, hypotension
Common: syncope

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