PRODUCT INFORMATION

VENTAVIS® iloprost 10 microgram/mL

NAME OF MEDICINE
Ventavis 10 microgram/mL nebuliser solution

Laboratory Code ZK 36374

CHEMICAL NAME: (E)-(3aS,4R,5R,6aS)-Hexahydro-5-hydroxy-4((E)-(3S,4RS)-3-hydroxy-4methyl-1-octen-6-ynyl)-Δ2(1H)δ-pentalenevaleric acid.
MOLECULAR FORMULA: C22H32 O4
MOLECULAR WEIGHT: 360.48
CAS NUMBER: 73873-87-7

DESCRIPTION
One ampoule with 2 mL nebuliser solution contains 26.8 microgram iloprost trometamol equivalent to 20 microgram iloprost, and the excipients trometamol, ethanol 96%, sodium chloride, hydrochloric acid and water for injections.

PHARMACOLOGY
Iloprost, the active ingredient of Ventavis, is a synthetic prostacyclin analog.
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.

Pharmacokinetics
- Absorption
When iloprost is administered via inhalation in patients with pulmonary hypertension (iloprost dose at the mouthpiece: 5 microgram), mean peak serum concentrations of 100 to 200 picogram/mL were observed at the end of inhalation. These concentrations decline with half-lives between approximately 5 and 25 minutes. Within 30 minutes to 1 hour after the end of inhalation, iloprost is not detectable in the central compartment (limit of quantification 25 picogram/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 protein binding of iloprost is concentration independent in the range of 30 to 3000 picogram/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.

Iloprost is extensively metabolised principally 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 suggest that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.

• **Elimination**

No studies performed following inhalation.

In subjects with normal renal and hepatic function, the disposition of iloprost following intravenous infusion is characterised 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 ³H-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 patients**

**Renal dysfunction:**

The pharmacokinetics of intravenous iloprost was investigated in an open label, comparative study in 21 patients with chronic renal failure (CRF) not on dialysis (Group 1) and patients with CRF on dialysis (Group 2).

Group 1 contained 10 patients with a mean creatinine clearance of 0.29±0.12 mL/min/kg, and Group 2 included 11 patients with a mean creatinine clearance of 0.16±0.05 mL/min/kg. Iloprost was administered as an intravenous infusion at a rate of 1ng/kg/min for 60 minutes. The mean results are shown in Table 1 below:
Table 1. Pharmacokinetics of intravenous iloprost in patients with renal dysfunction

<table>
<thead>
<tr>
<th>RENAL STUDY</th>
<th>NON-DIALYSIS</th>
<th>DIALYSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>7/10</td>
<td>8/11</td>
</tr>
<tr>
<td>Age (range)</td>
<td>23 - 73 years</td>
<td>25 - 74 years</td>
</tr>
<tr>
<td>Dose (ng/kg/min)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Plasma Conc. At 60min (pg/mL)</td>
<td>51 ± 11</td>
<td>193 ± 77</td>
</tr>
<tr>
<td>AUC α-phase (pg.h/mL)</td>
<td>42 ± 17</td>
<td>170 ± 95</td>
</tr>
<tr>
<td>T1/2 α-phase (h)</td>
<td>0.06 ± 0.01</td>
<td>0.055 ± 0.005</td>
</tr>
<tr>
<td>AUC β-phase (pg.h/mL)</td>
<td>12 ± 14</td>
<td>43 ± 36</td>
</tr>
<tr>
<td>T1/2 β-phase (h)</td>
<td>0.64 ± 0.35</td>
<td>0.59 ± 0.16</td>
</tr>
<tr>
<td>AUC (pg.h/mL)</td>
<td>54 ± 22</td>
<td>230 ± 103</td>
</tr>
<tr>
<td>Total Clearance (mL/min/kg)</td>
<td>17.6 ± 5.2</td>
<td>5.2 ± 2.2</td>
</tr>
</tbody>
</table>

α and β phases refer to biphasic disposition.

Patients with end stage renal failure undergoing intermittent dialysis treatment were 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). The half lives were similar in the two groups.

Hepatic dysfunction:

The pharmacokinetics of intravenous iloprost was investigated in an open labelled, uncontrolled study of 8 patients with liver impairment. The cirrhosis was of alcoholic origin in all cases except one which was cryptogenic. Five of the eight patients were Child Pugh Class B, two were Class C and one was Class A. Iloprost was given as an intravenous infusion at a rate of 1ng/kg/min for 60 minutes. The mean pharmacokinetic results compared with historical controls are given in Table 2 below:

Table 2. Pharmacokinetics of intravenous iloprost in patients with liver impairment

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Cirrhotic</th>
<th>Normal (historical control)</th>
<th>Normal (historical control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>8</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Age</td>
<td>56 ± 9 years</td>
<td>30 ± 8 years</td>
<td>59 ± 5years</td>
</tr>
<tr>
<td>Dose (ng/kg/min)</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Css (pg/mL)</td>
<td>93</td>
<td>46</td>
<td>135</td>
</tr>
<tr>
<td>Clearance (total) (mL/min/kg)</td>
<td>10 ± 5</td>
<td>21 ± 3</td>
<td>20 ± 5</td>
</tr>
<tr>
<td>t1/2 (min)</td>
<td>28 ± 24</td>
<td>20 ± 7</td>
<td>26 ± 7</td>
</tr>
</tbody>
</table>
Because iloprost is extensively metabolised by the liver, the plasma levels of the drug are influenced by changes in hepatic function. The mean clearance of iloprost in the study was 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 groups. There is no effect on t1/2.

Age and gender:
Gender is not of clinical relevance to the pharmacokinetics of iloprost. No pharmacokinetic data is available in elderly patients.

**CLINICAL TRIALS**
Clinical studies on the efficacy and safety of Ventavis solution for inhalation have been conducted. A phase II study (A00794) and a phase III study (A02997) comprise the main efficacy and safety data.

**Phase II Study (A00794)**
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.

Thirty patients were randomised to the iloprost group and 33 to the control group. Fifteen patients prematurely discontinued study medication (8 iloprost and 7 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 100 microgram (50 microgram – 150 microgram). During the long term study phase the median range daily dose was 100 microgram (range 50 microgram to 200 microgram).

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 dyspnoea 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 (A02997)

This was a multicentre double-blind randomised 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 30 microgram divided into 6 inhalations (range 12.5 microgram to 45 microgram). 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 patient from the iloprost group died after discontinuing the 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 dyspnoea 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.
Table 3. Overview of secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Iloprost (n = 101)</th>
<th>Placebo (n = 102)</th>
<th>Treatment Effect p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in NYHA class**</td>
<td>25 (24.8%)</td>
<td>13 (12.7%)</td>
<td>0.032 (4)</td>
</tr>
<tr>
<td>Improvement of WD of 10% vs. baseline**</td>
<td>38 (37.6%)</td>
<td>26 (25.5%)</td>
<td>NS (6)</td>
</tr>
<tr>
<td>Walking distance – change from baseline*#</td>
<td>22.2 ± 71.4</td>
<td>-3.3 ± 74.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 95</td>
<td>n = 85</td>
<td>0.032 (1)</td>
</tr>
<tr>
<td>Perceived exertion (RPE) scale*#</td>
<td>-0.38 ± 2.7</td>
<td>0.04 ± 2.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 95</td>
<td>n = 84</td>
<td>NS (6)</td>
</tr>
<tr>
<td>Deterioration(3)</td>
<td>5 (4.9%)</td>
<td>9 (8.8%)</td>
<td>NS (6)</td>
</tr>
<tr>
<td>Mortality until week 12(3)</td>
<td>1 (1.0%)</td>
<td>4 (3.9%)</td>
<td>NS (6)</td>
</tr>
<tr>
<td>Need for transplantation*</td>
<td>2 (2.0%)</td>
<td>4 (3.9%)</td>
<td>NS (6)</td>
</tr>
<tr>
<td>MDI focal score – change to baseline*</td>
<td>0.448 ± 1.691</td>
<td>0.174 ± 1.365</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 96</td>
<td>n = 86</td>
<td>NS (6)</td>
</tr>
<tr>
<td>MDI transition score*</td>
<td>1.42 ± 2.6</td>
<td>0.30 ± 2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 96</td>
<td>n = 86</td>
<td>0.015 (2)</td>
</tr>
<tr>
<td>EQ-VAS – change to baseline*</td>
<td>5.43 ± 17.32</td>
<td>-1.77 ± 18.95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 95</td>
<td>n = 82</td>
<td>0.016 (5)</td>
</tr>
</tbody>
</table>

* 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) NS = not significant

The HaloLite™ nebuliser system was used to administer Ventavis in the clinical trial.

INDICATIONS

Treatment of patients with primary pulmonary hypertension or secondary pulmonary hypertension due to connective tissue disease or drug-induced, in moderate or severe stages of the disease. In addition, treatment of moderate or severe secondary pulmonary hypertension due to chronic pulmonary thromboembolism, where surgery is not possible.

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, suspected pulmonary congestion, 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.

PRECAUTIONS

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.

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 or two hours).

Risk of syncope

Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope (see INTERACTIONS WITH OTHER MEDICINES). Syncope is also a common symptom of the disease itself. Patients who have a history of syncope in association with pulmonary hypertension should avoid any unusual straining, for example during exercise. Before exercise it might be useful to inhale Ventavis. The pulmonary vasodilatory effect of inhaled iloprost is short duration (one to two hours). The increased occurrence of syncopes can reflect insufficient therapeutic effect and/or deterioration of the underlying disease. The need to adapt and/or change the therapy should be considered. If syncope occurs on rising, it may be helpful to take the first dose of the day on waking, while still recumbent.

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 arterial pressure less than 85 mmHg.

Bronchospasm

Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperreactivity (see ADVERSE 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.

Pulmonary venous hypertension

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

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.

Patients with hepatic and renal impairment

Based on data with intravenously administered iloprost the elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis and a dose reduction may be considered. A cautious initial dose titration using dosing intervals of 3 - 4 hours is recommended. (see DOSAGE AND ADMINISTRATION and Pharmacokinetics).
Other
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.

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.

Paediatric use
The experience in children and adolescents (patients below 18 years of age) is limited. Therefore Ventavis is not recommended for use in this population (see DOSAGE AND ADMINISTRATION).

Effects on fertility
Fertility was not impaired in rats treated with up to 1 mg/kg/day IV and up to 34.4 mg/kg/day PO iloprost (approximately 600 times the clinical exposure based on AUC).

Use in pregnancy
Category B3
Women with pulmonary hypertension (PH) must avoid pregnancy as it may lead to life-threatening exacerbation of the disease.

There are no adequate data from the use of Ventavis in pregnant women. In embryo- and fetotoxicity studies in rats, continuous IV infusion of iloprost increased skeletal anomalies at 0.01-1 mg/kg/day (incomplete ossification and shortened digits of the forepaws) and embryofetal resorption at 1 mg/kg/day. Increased embryofetal resorption and/or incomplete ossification, but not shortened digits, were also observed in rats treated with 34.4 mg/kg/day iloprost by oral gavage (ca 600 times the clinical exposure based on AUC) or in rabbits treated with 0.5 mg/kg/day iloprost by continuous IV infusion or 5.6 mg/kg/day by oral gavage (ca 300 times the clinical exposure based on AUC). There was no evidence of embryofetal toxicity in a monkey study at up to 40 microgram/kg/day (9 fetuses examined at this dose) by continuous IV infusion (60 times the anticipated clinical exposure based on AUC). The gestation time in rats was also prolonged slightly at 1 mg/kg/day by continuous IV infusion.

The potential risk to humans is not known. There are no adequate and well-controlled studies in pregnant women. The limited amount of data regarding safety of inhaled iloprost in pregnancy, to both the pregnant woman and the unborn child, is based on the experience of a small number of women exposed during pregnancy, and a small number of paediatric cases exposed in utero, reported to the sponsor and in the published literature. Therefore women of child bearing potential should use effective contraceptive measures during treatment with Ventavis. If pregnancy occurs, Ventavis should only be used following careful risk-benefit evaluation.

Use in lactation
Low levels of iloprost or its metabolites are excreted into milk by lactating rats. Pup viability was reduced when lactating rats were treated with 1 mg/kg/day iloprost by continuous IV infusion or 34.4 mg/kg/day by oral gavage, with no effects on postnatal development at 0.1 mg/kg/day IV (68 times the clinical exposure based on AUC) and 0.7 mg/kg/day PO (20 times the clinical exposure based on AUC). There are no human data on the excretion of iloprost/metabolites into human breast milk or on the safety of
Ventavis exposure in infants. There are no adequate and well-controlled studies to support the efficacy and safety in lactating women. Therefore women should not breastfeed during treatment with Ventavis.

**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, ability to drive or operate machines may be seriously affected.

**Mutagenicity**

Iloprost is not a mutagen in bacterial and mammalian cells *in vitro*, and in the micronucleus test *in vivo*.

**Carcinogenicity**

There have been no carcinogenicity studies by the inhalation route. No tumourigenic potential was demonstrated in carcinogenicity studies in mice and rats dosed orally with up to 16 mg/kg/day iloprost for 22-24 months (9-12 times the clinical exposure based on $C_{\text{max}}$).

**INTERACTIONS WITH OTHER MEDICINES**

Iloprost may increase the antihypertensive effect of vasodilating and antihypertensive agents. 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 [e.g., theophylline, pentoxifylline, dipyridamole], selective phosphodiesterase 3 [PDE3] inhibitors [e.g., milrinone, cilostazol, anagrelide] and nitrovasodilators) may enhance iloprost-mediated platelet inhibition, thereby increasing the risk of bleeding (see ADVERSE EFFECTS). If bleeding occurs, iloprost administration should be stopped. Careful monitoring of the patients taking anticoagulants or 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. 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. In an animal study, it was found that iloprost may result in a reduction in t-PA steady-state plasma concentration.

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

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 expected.

**ADVERSE 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 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.

The adverse drug reactions (ADRs) reported below are based on clinical trial data involving 131 patients taking the medication. The frequencies of ADRs are defined as:

- **Very common**: ≥1/10
- **Common**: ≥1/100 to <1/10
- **Uncommon**: ≥1/1,000 to <1/100
- **Rare**: ≥1/10,000 to <1/1,000
- **Very rare**: <1/10,000

### Table 4. Adverse drug reactions reported based on clinical trial data

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Bleeding events*§</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Tachycardia, Palpitations</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Vasodilation</td>
<td>Hypotension*, Syncope*</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Chest pain, Cough</td>
<td>Dyspnoea, Pharyngolaryngeal pain, Throat irritations</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Diarrhoea, Vomiting, Mouth and tongue irritation including pain</td>
</tr>
<tr>
<td>Skin and subcutaneous skin disorders</td>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in jaw / trismus</td>
<td>Back pain</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Peripheral oedema</td>
<td></td>
</tr>
</tbody>
</table>

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

§ Bleeding events (mostly epistaxis and haemoptysis) 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 INTERACTIONS
WITH OTHER MEDICINES). Fatal cases of cerebral and intracranial haemorrhage have been reported.

'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.

As expected in patients with pulmonary hypertension, syncopes were common, and did not differ significantly between the treatment groups in frequency (see PRECAUTIONS).

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

Post-marketing adverse events
Hypersensitivity, bronchospasm*, dysgeusia, thrombocytopenia, wheezing and nasal congestion have also been reported in patients treated with Ventavis. (see PRECAUTIONS – bronchial hyperreactivity).

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

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.

DOSAGE AND ADMINISTRATION
The solution is administered with a suitable inhalation device (nebuliser) as recommended in instruction for use and handling. Previous therapy should be adjusted to individual needs (see Interactions with other medicines). In order for the correct dose of iloprost to be delivered to the patient a suitable nebuliser must be used. The HaloLite nebuliser described in the Clinical Trial section is not currently available in Australia. Clinical data on the use of other similar nebulisers with Ventavis is not available.

Ventavis nebuliser solution should not come into contact with skin and eyes, oral ingestion of Ventavis solution should be avoided.
Recommended dose:

- Adults
At initiation of Ventavis 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 during waking hours 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.

- Patients with hepatic impairment
Iloprost elimination is reduced in patients with hepatic dysfunction. 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 microgram should be administered with dosing intervals of 3 - 4 hours (corresponds to administration of max. 6 times per day during waking hours). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a further increase in the dose up to 5.0 microgram 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 ≤ 30 mL/min were not investigated in the clinical trials. Based on data with intravenously administered iloprost the elimination is reduced in patients with renal failure requiring dialysis. Caution should be exercised in treating patients with severe renal failure. Therefore, the same dosing recommendations as in patients with hepatic impairment are to be applied (For dosing recommendations, see "Patients with hepatic impairment" above).

- Paediatric patients/ Children and adolescents (below 18 years of age)
The experience in children and adolescents (patients below 18 years of age) is limited. Therefore Ventavis is not recommended for use in this population (see PRECAUTIONS).

- 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.

Instructions for use/handling
For each inhalation session a new ampoule of Ventavis should be used. The content of the opened 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 nebulisers provided by the device manufacturers should be followed carefully.

Use with nebulisers:

In general suitable nebulisers to be used for the inhalation therapy with Ventavis nebuliser solution are CE certified and work with compressed air.

Nebulisers suitable for inhalation of iloprost should deliver 2.5 microgram or 5 microgram iloprost at the mouthpiece in a time period of approximately 4 to 10 minutes. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol is between 2 and 4 micrometers. The respirable range of particles is 1 – 5 micrometers. To minimise accidental exposure, it is recommended to use Ventavis with nebulisers with a filter or inhalation-triggered systems, and to keep the room well ventilated.

Nebuliser systems should be checked with the manufacturer of the nebuliser to ensure compliance with the above requirements of MMAD before use with Ventavis.

If switching to a different type of nebuliser supervision by the treating physician is necessary.

Incompatibilities

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

OVERDOSAGE

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, diarrhoea and limb pain might also be possible.

- Therapy

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

Contact Poisons Information Centre 131126 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Ampoules of 3 mL, colourless, glass type I, containing 2 mL nebuliser solution.

Each ampoule contains 20 microgram iloprost.

Pack containing 6 or 30 ampoules.

Store below 30°C

Shelf life

Shelf life is 2 years when stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Bayer Australia Ltd
A.B.N. 22 000 138 714
875 Pacific Highway
PYMBLE NSW 2073
POISONS SCHEDULE OF THE MEDICINE
S4

DATE OF FIRST INCLUSION IN THE ARTG
21 January 2004

DATE OF MOST RECENT AMENDMENT
16 June 2017

© Registered Trademark of the Bayer Group, Germany