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 ampoule with 1 ml solution contains 10 micrograms iloprost.
Each ampoule with 2 ml solution contains 20 micrograms iloprost.

Excipient: Ethanol 96% 0.81 mg per ml.
For a full list of excipients, see section 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 (see section 6.6).

Concomitant therapy should be adjusted to individual needs (see section 4.5 Interaction with other medicaments and other forms of interaction).

**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), starting with the low dose of 2.5 microgram for the first inhalation, followed by 5.0 micrograms for the second inhalation. In case of poor tolerability of the 5.0 microgram dose, the dose should be reduced to 2.5 micrograms.

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 micrometres. 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.
<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated inhalation time (frequency of 15 breaths per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HaloLite</td>
<td>2.5 micrograms 5 micrograms</td>
<td>4 to 5 min 8 to 10 min</td>
</tr>
<tr>
<td>Prodose</td>
<td>2.5 micrograms 5 micrograms</td>
<td>4 to 5 min 8 to 10 min</td>
</tr>
</tbody>
</table>

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).

Venta-Neb, 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 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.

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.

<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated Inhalation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venta-Neb</td>
<td>2.5 micrograms 5 micrograms</td>
<td>4 min 8 min</td>
</tr>
</tbody>
</table>

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 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, showing two coloured rings (white-yellow), will be transferred into the appropriate nebuliser medication chamber immediately before use.
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 (see section 5.2), patients stabilized on one nebuliser should not switch to another nebuliser without supervision by the treating physician.

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 micrograms 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 micrograms 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. 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

There is no experience with Ventavis in children or adolescents.
4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Pregnancy and lactation (see section 4.6).
- 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.

Blood pressure should be checked while initiating Ventavis. In patients with low systemic blood pressure and in patients with postural hypotension or receiving drugs 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 alert to the presence of concomitant conditions or drugs that might increase the risk of hypotension and syncope (see section 4.5).

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 syncopes can reflect therapeutical 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).

Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperactivity (see section 4.8 Undesirable effects). 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.

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.

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 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 (such as HaloLite/Prodose, I-Neb), 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 effects of vasodilatators and antihypertensive agents and then favour the risk of hypotension (see section 4.4). Should significant hypotension occur this can be corrected by dose reduction of iloprost.

Since 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 medicinal products, ticlopidine, clopidogrel, 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. 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 **Fertility, pregnancy and lactation**

*Women of child-bearing potential*

The potential risk for humans is unknown. Therefore, women of child-bearing potential should use effective contraceptive measures during treatment.

*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. Iloprost must not be administered to pregnant women (see section 4.3 Contraindications).

*Breast-feeding*

It is not known whether iloprost/metabolites are excreted in human breast milk. The medicinal product must not be administered to breast feeding mothers (see section 4.3 Contraindications).

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 ability to drive or operate machines may be seriously 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 most common adverse reactions seen in clinical trials include vasodilatation (including hypotension), headache and increased cough.

The adverse reactions reported below are based on pooled clinical trial data from phase II and III clinical trials involving 131 patients taking the medication. The frequencies of ADRs are defined as 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 from clinical trial data, are listed under "Frequency not known".

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

<table>
<thead>
<tr>
<th>System organ class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Frequency not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Vasodilatation</td>
<td>Syncope (see section 4.4),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Bleeding events*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Chest discomfort / chest pain</td>
<td>Dyspnoea Pharyngolaryngeal pain and throat irritation</td>
<td>Bronchospasm (see section 4.4) / Wheezing</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>Nausea</td>
<td>Diarrhoea Vomiting Mouth and tongue irritation</td>
<td>Dysgueusia</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Pain in jaw/trismus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous skin disorders</td>
<td></td>
<td>Rash</td>
<td></td>
</tr>
</tbody>
</table>

* Bleeding events were very common as expected in this patient population with a high proportion of patients taking anticoagulant co-medication (see section 4.5).

Syncope is a common symptom of the disease itself, but can also occur under therapy. The increased occurrence of synapes can be related to the deterioration of the disease or insufficient effectiveness of the product (see section 4.4).

Peripheral oedema is a very common symptom of the disease itself, but can also occur under therapy. The occurrence of peripheral oedema can be related to the deterioration of the disease or insufficient effectiveness of the product.
4.9 Overdose

- Symptoms

No case of overdose has been reported. In the case of an overdose hypotensive/vasovagal reaction might be anticipated as well as headache, flushing, nausea, vomiting, and diarrhoea. An increase of blood pressure, bradycardia or tachycardia and limb or back pain might be possible.

- Therapy

A specific antidote is not known. Interruption of the inhalation session, monitoring and symptomatic measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01AC11

This medicinal product has been authorised under “Exceptional Circumstances”. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency (EMA) will review any new information which may become available every year and this SPC will be updated as necessary.

Iloprost, the active substance of Ventavis, is a synthetic prostacyclin analogue. The following pharmacological effects have been observed in vitro:

- Inhibition of platelet aggregation, platelet adhesion and release reaction
- Dilatation of arterioles and venules
- Increase of capillary density and reduction of increased vascular permeability caused by mediators such as serotonin or histamine in the microcirculation
- Stimulation of endogenous fibrinolytic potential

The pharmacological effects after inhalation of Ventavis are:

Direct vasodilatation of the pulmonary arterial bed occur with consecutive significant improvement of pulmonary artery pressure, pulmonary vascular resistance and cardiac output as well as mixed venous oxygen saturation.

In a small, randomized, 12-week double-blinded phase, placebo-controlled study (the STEP trial), 34 patients treated with bosentan 125 mg twice per day for at least 16 weeks who were in stable haemodynamic conditions before enrolment, tolerated the addition of inhaled iloprost (up to 5 microgram 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 microgram and the mean number of inhalations per day was 5.6. The acute adverse effects in patients receiving concomitant bosentan and iloprost were consistent with those observed in the larger experience of the phase 3 study in patients receiving only iloprost. No reliable conclusion could be drawn on efficacy of the association as the sample size was limited and the study was of short duration.

No clinical trial data are available comparing directly in intra-patient observations the acute haemodynamic response after intravenous to that after inhaled iloprost. The haemodynamics observed suggest an acute response with preferential effect of inhaled treatment on the pulmonary vessels. The pulmonary vasodilatory effect of each single inhalation levels off within one to two hours.
However, the predictive value of these acute haemodynamic data are considered to be of limited value as acute response does not in all cases correlate with long-term benefit of treatment with inhaled iloprost.

- **Efficacy in adult patients with pulmonary hypertension**

A randomised, double-blind, multi-centre, placebo-controlled phase III trial (study RRA02997) has been conducted in 203 adult patients (inhaled iloprost: N=101; placebo n=102) with stable pulmonary hypertension. Inhaled iloprost (or placebo) was added to patients' current therapy, which could include a combination of anticoagulants, vasodilators (e.g. calcium channel blockers), diuretics, oxygen, and digitalis, but not PGI2 (prostacyclin or its analogues). 108 of the patients included were diagnosed with primary pulmonary hypertension, 95 were diagnosed with secondary pulmonary hypertension of which 56 were associated with chronic thromboembolic disease, 34 with connective tissue disease (including CREST and scleroderma) and 4 were considered appetite suppressant drug related. The baseline 6-minute walk test values reflected a moderate exercise limitation: in the iloprost group the mean was 332 meters (median value: 340 meters) and in the placebo group the mean was 315 meters (median value: 321 meters). In the iloprost group, the median daily inhaled dose was 30 micrograms (range 12.5 to 45 micrograms/day). The primary efficacy endpoint defined for this study, was a combined response criterion consisting of improvement in exercise capacity (6 minute walk test) at 12 weeks by at least 10% versus baseline, and improvement by at least one NYHA class at 12 weeks versus baseline, and no deterioration of pulmonary hypertension or death at any time before 12 weeks. The rate of responders to iloprost was 16.8% (17/101) and the rate of responders in the placebo group was 4.9% (5/102) (p=0.007).

In the iloprost group, the mean change from baseline after 12 weeks of treatment in the 6 minute walking distance was an increase of 22 meters (-3.3 meters in the placebo group, no data imputation for death or missing values).

In the iloprost group the NYHA class was improved in 26% of patients (placebo: 15%) (p = 0.032), unchanged in 67.7% of patients (placebo: 76%) and deteriorated in 6.3% of patients (placebo: 9%). Invasive haemodynamic parameters were assessed at baseline and after 12 weeks treatment.

A subgroup analysis showed that no treatment effect was observed as compared to placebo on the 6-minute walk test in the subgroup of patients with secondary pulmonary hypertension. A mean increase in the 6-minute walk test of 44.7 meters from a baseline mean value of 329 meters vs. a change of -7.4 meters from a baseline mean value of 324 meters in the placebo group (no data imputation for death or missing values) was observed in the subgroup of 49 patients with primary pulmonary hypertension receiving treatment of inhaled iloprost for 12 weeks (46 patients in the placebo group).

No study has been performed with Ventavis in children with pulmonary hypertension.

5.2 Pharmacokinetic properties

- Absorption

When iloprost is administered via inhalation in patients with pulmonary hypertension (iloprost dose at the mouthpiece: 5 micrograms), peak serum levels of 100 to 200 picograms/ml were observed at the end of inhalation session. These levels 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 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 protein 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 performed following inhalation.

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. Results of in vitro studies reveal that CYP 450-dependent metabolism plays only a minor role in the biotransformation of iloprost. Further 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 urine in 2 phases, for which half-lives of about 2 and 5 hours (plasma) and 2 and 18 hours (urine) have been calculated.

• Pharmacokinetics after use with different nebulisers

In a randomized, crossover study with 20 healthy adult men, pharmacokinetics was investigated following inhalation of Ventavis (5 mcg iloprost) by the I-Neb AAD in comparison to the ProDose (5 mcg disk).

Higher maximum serum level (Cmax) and systemic exposure (AUC(0-tlast)) as well as a shorter time to reach maximum serum concentration (tmax) were found following Ventavis inhalation via the I-Neb AAD in comparison to the ProDose nebulizer. The pharmacokinetic results reflect the slightly different in vitro characteristics of these nebulizers (see Section 4.2).
Pharmacokinetic parameters of iloprost after inhalation of 5 mcg iloprost by I-Neb AAD vs. ProDose

<table>
<thead>
<tr>
<th></th>
<th>Cmax (pg/mL)</th>
<th>t max (h), median (range)</th>
<th>AUC(0-tlast) (pg·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>geometric mean (CV%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I-Neb</td>
<td>119 (41.2%)</td>
<td>0.147 (0.086 – 0.268)</td>
<td>28.9 (47.4%)</td>
</tr>
<tr>
<td>ProDose</td>
<td>80.0 (46.7%)</td>
<td>0.183 (0.133 – 0.279)</td>
<td>18.7 (50.5%)</td>
</tr>
</tbody>
</table>

AUC(0-tlast) = Area under the concentration time curve from 0h data point up to last measurable serum level

CV = coefficient of variation

- Characteristics in patients

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 metabolised by the liver, the plasma levels of the active substance 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.

Age and gender:

Age and gender are not of clinical relevance to the pharmacokinetics of iloprost.

5.3 Preclinical safety data

- Systemic toxicity

In acute toxicity studies, single intravenous and oral doses of iloprost caused severe symptoms of intoxication or death (IV) at doses about two orders of magnitude above the intravenous therapeutic dose. Considering the high pharmacological potency of iloprost and the absolute doses required for therapeutic purposes the results obtained in acute toxicity studies do not indicate a risk of acute adverse effects in humans. As expected for a prostacyclin, iloprost produced haemodynamic effects (vasodilatation, reddening of skin, hypotension, inhibition of platelet function, respiratory distress) and general signs of intoxication such as apathy, gait disturbances, and postural changes.

Continuous IV/SC infusion of iloprost up to 26 weeks in rodents and non-rodents did not cause any organ toxicity at dose levels which exceeded the human therapeutic systemic exposure between 14 and 47 times (based on plasma levels). Only expected pharmacological effects like hypotension, reddening of skin, dyspnoea, increased intestinal motility were observed.

Based on Cmax values in rats the systemic exposure in these parenteral studies was approximately 3.5 times higher than the maximum achievable exposure after inhalation. This highest achievable dose of 48.7 micrograms/kg/day was also the “no observed adverse effect level” (NOAEL) as evaluated in inhalation toxicity studies in rats up to 26 weeks. Following inhalation the systemic exposure based on
AUC values in rats exceeded the corresponding therapeutic exposure in human patients by approximately 13 times.

- Genotoxic potential, tumorigenicity

*In vitro* (bacterial, mammalian cells, human lymphocytes) and *in vivo* studies (micronucleus test) for genotoxic effects have not produced any evidence for a mutagenic potential. No tumorigenic potential of iloprost was observed in tumorigenicity studies in rats and mice.

- Reproduction toxicology

In embryo- and foetotoxicity studies in rats continuous intravenous administration of iloprost led to anomalies of single phalanges of the forepaws in a few foetuses/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 haemodynamic alterations in the foetoplacental unit. In comparable embryotoxicity studies in rabbits and monkeys no such digit anomalies or other gross-structural abnormalities were observed. In rats, passage of extremely low levels of iloprost into the milk was observed.

- Local tolerance, contact sensitising and antigenicity potential

In inhalation studies in rats, the administration of an iloprost formulation with a concentration of 20 micrograms/ml up to 26 weeks did not cause any local irritation of the upper and lower respiratory tract.

A dermal sensitisation (maximisation test) and an antigenicity study in guinea pigs showed no sensitising potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol, Ethanol 96 %, Sodium chloride, Hydrochloric acid (for pH adjustment), Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
6.5 Nature and contents of container

1-ml ampoules, colourless, glass type I, containing 1 ml nebuliser solution, ring coded with two
coloured rings (white - yellow).
3-ml ampoules, colourless, glass type I, containing 2 ml nebuliser solution, ring coded with two
coloured rings (white – pink).

1 ml nebuliser solution:
Packages containing 30 or 168 ampoules.

2 ml nebuliser solution:
Packages containing 30, 90, 100 or 300 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For each inhalation session the contents of one opened ampoule of Ventavis has to be transferred
completely into the nebuliser medication chamber immediately before use.

After each inhalation session, any solution remaining in the nebuliser should be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Schering Pharma AG
D-13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/255/001
EU/1/03/255/002
EU/1/03/255/003
EU/1/03/255/004
EU/1/03/255/005
EU/1/03/255/006
EU/1/03/255/007
EU/1/03/255/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 September 2003
Date of last renewal: 16 September 2008

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines
ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER
A. MANUFACTURING AUTHORITY HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Berlimed. S.A., Poligono Industrial Santa Rosa s/n, 28806 Alcalá de Henares, Madrid, Spain

B. CONDITIONS OF THE MARKETING AUTHORITY

- CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORITY HOLDER

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

- CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

- OTHER CONDITIONS

The Marketing Authorisation Holder will submit yearly PSURs unless otherwise specified by the CHMP.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORITY HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

Clinical aspects:

In July 2004, the CHMP and MAH agreed on a protocol for an observational study 308120 to gather longer-term data on the safety and efficacy of Ventavis (iloprost). The first patient will be enrolled by April 2005 the latest. Progress reports will be provided together with the submission of the PSURs. A final study report will be provided within 6 months after last patient completed and forwarded for review by CHMP, estimated dated of 4Q 2012.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
(PACK WITH 30 AMPOULES IN A CARTON WITH 90 (3 x 30) AMPOULES WITH 2 ML)
(PACK WITH 30 AMPOULES IN A CARTON WITH 300 (10 x 30) AMPOULES WITH 2 ML)

1. NAME OF THE MEDICINAL PRODUCT

Ventavis 10 microgram/ml, Nebuliser solution
Iloprost

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ampoule with 2 ml contains 20 micrograms iloprost (as iloprost trometamol).

3. LIST OF EXCIPIENTS

Excipients:
trometamol, ethanol 96 %, sodium chloride, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution.
30 ampoules with 2 ml.
Part of a box containing 90 ampoules with 2 ml. No individual sale of single packs.
Part of a box containing 300 ampoules with 2 ml. No individual sale of single packs.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Schering Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/255/007 [90 (3 x 30) x 2 ml]
EU/1/03/255/008 [300 (10 x 30) x 2 ml]

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ventavis 2 ml
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

(OUTER CARTON /
30 AMPOULES WITH 2 ML
90 AMPOULES WITH 2 ML
90 (3 x 30) AMPOULES WITH 2 ML
100 AMPOULES WITH 2 ML
300 AMPOULES WITH 2 ML
300 (10 x 30) AMPOULES WITH 2 ML)

1. NAME OF THE MEDICINAL PRODUCT

Ventavis 10 microgram/ml nebuliser solution
Iloprost

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients:
trometamol, ethanol 96 %, sodium chloride, hydrochloric acid (for pH adjustment), water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution.
30 ampoules with 2 ml
90 ampoules with 2 ml
90 (3 x 30) ampoules with 2 ml
100 ampoules with 2 ml
300 ampoules with 2 ml
300 (10 x 30) ampoules with 2 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY
8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Schering Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/255/001 [30 x 2 ml]
EU/1/03/255/006 [90 x 2 ml]
EU/1/03/255/007 [90 (3 x 30) x 2 ml]
EU/1/03/255/002 [100 x 2 ml]
EU/1/03/255/003 [300 x 2 ml]
EU/1/03/255/008 [300 (10 x 30) x 2 ml]

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ventavis 2 ml
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
(PACK WITH 42 AMPOULES IN A CARTON WITH 168 (4 x 42) AMPOULES WITH 1 ML)

1. NAME OF THE MEDICINAL PRODUCT
Ventavis 10 microgram/ml, Nebuliser solution
Iloprost

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each ampoule with 1 ml contains 10 micrograms iloprost (as iloprost trometamol).

3. LIST OF EXCIPIENTS
Excipients:
trometamol, ethanol 96 %, sodium chloride, hydrochloric acid (for pH adjustment), water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS
Nebuliser solution.
42 ampoules with 1 ml.
Part of a box containing 168 ampoules with 1 ml. No individual sale of single packs.

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Inhalation use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN
Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Schering Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/255/005

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ventavis 1 ml
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

(OUTER CARTON /
 30 AMPOULES WITH 1 ML
168 AMPOULES WITH 1 ML)

1. NAME OF THE MEDICINAL PRODUCT

Ventavis 10 microgram/ml, Nebuliser solution
Iloprost

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ampoule with 1 ml contains 10 micrograms iloprost (as iloprost trometamol).

3. LIST OF EXCIPIENTS

Excipients:
trometamol, ethanol 96 %, sodium chloride, hydrochloric acid (for pH adjustment), water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution.
30 ampoules with 1 ml.
168 ampoules with 1 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Inhalation use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Schering Pharma AG
D-13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/255/004 [30 x 1 ml]
EU/1/03/255/005 [168 x 1 ml]

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

For the administration with the I-Neb nebuliser.

16. INFORMATION IN BRAILLE

Ventavis 1 ml
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

(AMPOULE WITH 2 ML)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ventavis 10 microgram/ml nebuliser solution
Iloprost
Inhalation use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 ml

6. OTHER
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
(AMPOULE WITH 1 ML)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ventavis 10 microgram/ml nebuliser solution
Illoprost
Inhalation use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml

6. OTHER
B. PACKAGE LEAFLET
Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Ventavis is and what it is used for
2. Before you use Ventavis
3. How to use Ventavis
4. Possible side effects
5. How to store Ventavis
6. Further information

1. WHAT VENTAVIS IS AND WHAT IT IS USED FOR

What Ventavis is

Ventavis is a nebuliser solution. The solution is changed into an aerosol mist by a special machine called a nebuliser.

What Ventavis is used for

Ventavis is used to treat moderate cases of primary pulmonary hypertension (PPH). This is a condition where blood pressure is too high in the blood vessels between the heart and the lungs.

How Ventavis works

The active substance of Ventavis (iloprost) imitates a natural substance in the body called prostacyclin. Ventavis and prostacyclin inhibit unwanted blocking or narrowing of blood vessels and allow more blood to flow through the vessels.

Breathing in the mist carries Ventavis to the lungs, where it can work most effectively in the artery between heart and lungs. Improved blood flow leads to a better supply of oxygen to the body and reduced strain on the heart.
2. BEFORE YOU USE VENTAVIS

Do NOT use Ventavis if you:

- **are allergic** (*hypersensitive*) to iloprost or any of the other ingredients of Ventavis (see also section 6. Further information).
- **are at risk of bleeding** – for example, if you have an active ulcer of the stomach or of the first part of the small intestine (*duodenal ulcers*), if you have suffered an injury, if you are at risk of bleeding within the skull.
- **have the disease due to a blocked or narrowed vein** (*venous occlusive disease*).
- **have had a stroke within the last 3 months**, or any other occurrence that reduced the blood supply to the brain (e.g. *transient ischemic attack*).
- **have a heart problem**, such as:
  - a heart attack within the last six months
  - severe changes in heart rate
  - poor blood flow to the heart muscles (*severe coronary heart disease* or *unstable angina*). Symptoms can be chest pain.
  - a weak heart (*decompensated cardiac failure*) which is not under close medical observation.
  - a defect of the heart valves that causes the heart to work poorly (*not related to pulmonary hypertension*).
- **are pregnant or breast-feeding**.

Take special care with Ventavis:

- Inhaling Ventavis might trigger breathing difficulties (see section 4.), especially in patients with bronchospasm (sudden constriction of the muscles in the walls of the small airways) and wheezing. Tell your doctor, **if you have a lung infection, severe asthma, or chronic lung disease**. (*chronic obstructive pulmonary disease*). Your doctor will closely monitor you.
- **If your blood pressure is too low** (less than 85 mmHg for the upper value) you should not start the therapy with Ventavis.
- In general, you will need to **take special care to try and avoid effects of low blood pressure**, such as fainting and dizziness:
  - Tell your doctor if you are taking any other medication because the combined effect with Ventavis may further lower your blood pressure (see below "Taking or using other medicines").
  - Stand up slowly when you get out of chairs or bed.
  - If you tend to faint as soon as you get out of bed, it may be helpful to take your first dose of the day while you are still lying down.
  - If you tend to experience fainting episodes, avoid any exceptional straining, for example during physical exertion; it might be useful to inhale Ventavis before. Fainting episodes may be due to the underlying disease. Tell your doctor if they get worse. He/she may consider adjusting your dose or changing your treatment.
- **If you suffer from a weak heart condition such as a right heart failure, and feel that your disease is worsening**, tell your doctor. Symptoms can be swelling of feet and ankles, shortness of breath, palpitations, urinating more frequently at night. Your doctor will consider changing your treatment.
- **If you experience difficulty breathing, cough up blood, and/or sweat excessively** these may be **signs that you have water in the lungs** (*lung oedema*). Stop using Ventavis and tell your doctor immediately. He/she will look for the cause and take appropriate measures.
- **If you have liver problems or very severe kidney problems, requiring dialysis**, tell your doctor. You may be gradually introduced to the prescribed dose or be prescribed a lower dose of Ventavis than for other patients (see section 3. "How to use Ventavis").
**Contact of Ventavis with skin or swallowing Ventavis:**

Do NOT let Ventavis solution come into contact with your skin or eyes. If it does, rinse the skin or your eyes immediately with plenty of water.

Do NOT drink or swallow Ventavis solution. If you swallow it accidentally, drink plenty of water and tell your doctor.

**Taking or using other medicines**

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Ventavis and certain other medicines may affect each other in the way they work in your body. Tell your doctor if you are taking:

- **Medicines used to treat high blood pressure or heart disease** (e.g. beta blockers, nitrovasodilators, ACE inhibitors). Your blood pressure may drop much further. Your doctor may change the dosage.
- **Medicines that thin the blood or inhibit blood clotting**, this includes acetylsalicylic acid - to lower fever and relieve pain, and heparin, coumarin-type anticoagulants [e.g. warfarin, phenprocoumon] as well as others.

Ask your doctor or pharmacist for advice before taking any medicine. He/she has more information on medicines to be careful with or avoid when using Ventavis.

**Using Ventavis with food and drink:**

Food or drink is not expected to affect Ventavis. However, you should avoid taking food or drink during inhalation.

**Pregnancy:**

- **If you are pregnant, or think you might be**, tell your doctor straight away. Ventavis must not be used by pregnant women (see section 2. Do not use Ventavis).
- **If you could get pregnant**, use reliable contraception from the time you start treatment and during treatment (ask your doctor).

**Breast-feeding:**

Stop breast-feeding when you start treatment. Ventavis must not be given to women who are breast-feeding, since it is not known whether the active substance is passed on through breast milk.

*Ask your doctor or pharmacist for advice before taking any medicine.*

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

These persons should not remain in a closed room where Ventavis is being administered to a patient.
Driving and using machines:

Ventavis lowers blood pressure and may cause dizziness or light-headedness in some people. Do not drive or operate any tools or machines if you feel these effects.

Important information about some of the ingredients of Ventavis:

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

3. HOW TO USE VENTAVIS

How to use Ventavis:

Always take Ventavis exactly as your doctor has told you.
- Ventavis nebuliser solution is inhaled using the nebulisers your doctor prescribed (either the HaloLite, the Prodose, the Venta-Neb or the I-Neb AAD system).
- The nebuliser turns Ventavis solution into a mist which you breathe in through your mouth.
- For the inhalation you should use a mouthpiece to prevent Ventavis coming into contact with your skin. Do not use a facial mask.
- Follow carefully any extra instructions that come with the nebuliser. Check with your doctor or pharmacist if you are unsure.
- Dispose of any Ventavis solution that you do not use in one inhalation session (see Section 5).

Use in children and adolescents:

Ventavis is not recommended for children or adolescents.

Caution:

Do not let Ventavis solution come into contact with your skin or eyes. If it does, rinse the skin or your eyes immediately with water.
Do not drink Ventavis solution. If you swallow it by accident, drink plenty of water and contact your doctor (see also “If you take more Ventavis than you should”).

How much to inhale and for how long:

- The dose of Ventavis and the duration of treatment that is right for you depends on your individual condition. Your doctor will advise you.
- Most people will have 6 to 9 inhalation sessions spread throughout the day. One inhalation session will usually last about 4 to 10 minutes depending on the prescribed dose.
- If you have liver problems or very severe kidney problems, your doctor will introduce you to Ventavis gradually and possibly prescribe fewer daily inhalations.
- If you feel that the effect of Ventavis is too strong or too weak, talk to your doctor or pharmacist.
- Ask your doctor to have someone help you become thoroughly familiar with the use of the nebuliser. You should not switch to another nebuliser without consulting the doctor who is treating you.
Room ventilation

Be sure to ventilate or air the room in which you have taken your Ventavis treatment. Other persons might accidentally be exposed to Ventavis through the room air. In particular, newborns, infants, and pregnant women should not be subjected to Ventavis.

**For HaloLite and ProDose systems:**

1. Just before you start to inhale, break open the glass ampoule containing 2 ml solution, which shows two coloured rings (white-pink), and transfer the complete contents into the nebuliser medication chamber.
2. You should run the inhalation cycle twice if you require a high dose (5 micrograms) and once if you require a low dose (2.5 micrograms). Independent of the dose the filling volume is always the contents of one glass container.
3. The inhalation time depends on your breathing pattern.

<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated Inhalation time (frequency of 15 breaths per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HaloLite</td>
<td>2.5 micrograms</td>
<td>4 to 5 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>8 to 10 min</td>
</tr>
<tr>
<td>Prodose</td>
<td>2.5 micrograms</td>
<td>4 to 5 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>8 to 10 min</td>
</tr>
</tbody>
</table>

**For the Venta-Neb system:**

1. Just before you start to inhale, break open the glass container and transfer the complete contents into the nebuliser medication chamber.
2. Two programs can be operated:
3. Your doctor will adjust Venta-Neb to the program you need to receive the dose prescribed for you.
   - 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.
4. You should use the green baffle plate to obtain the optimal droplet size for the administration of Ventavis.

<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated Inhalation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venta-Neb</td>
<td>2.5 micrograms</td>
<td>4 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>8 min</td>
</tr>
</tbody>
</table>

**For the I-Neb AAD system:**

1. Just before you start to inhale, break open the glass ampoule containing 1 ml solution, which shows two coloured rings (white - yellow), and transfer the complete contents into the nebuliser medication chamber.
2. The pre-set dose provided by the I-Neb AAD system is controlled by the medication chamber in combination with 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.
3. In order to ensure that you receive the prescribed dose, check the colour of the medication chamber and the colour of the control disc.
They should both have the same colour, either red for the 2.5 microgram dose or purple for the 5 microgram dose.
<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated Inhalation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-Neb AAD</td>
<td>2.5 micrograms</td>
<td>3.2 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>6.5 min</td>
</tr>
</tbody>
</table>

For further details please refer to the instruction manual of the nebuliser device or ask your doctor.

**If you use more Ventavis than you should:**

Using more Ventavis than you should may lead to a decrease in blood pressure with symptoms such as dizziness or fainting. You may also experience headache, reddening of the face (flushing), feeling sick (nausea), vomiting or diarrhoea. An increase in blood pressure, reduced or increased heart rate and limb or back pain may also be possible. If any of these happens:

- stop the inhalation session
- talk to your doctor

**If you forget to use Ventavis:**

You should not take a double dose to make up for a forgotten dose. Please ask your doctor what you should do.

**If you stop taking Ventavis:**

If you stop or wish to stop treatment, discuss it with your doctor first.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Ventavis can cause side effects, although not everybody gets them.

**Very common:** affects more than 1 user in 10.

**Common:** affects 1 to 10 users in 100.

**Frequency not known:** frequency can not be estimated from the available data

The following side effects may occur. In this case ask your doctor

- Fainting (*syncope*) is a common symptom of the illness itself but can also occur during treatment with Ventavis. *(see also section 2 "Take special care with Ventavis", for advice on what you can do to try and avoid this)*.
- Common: low blood pressure (*hypotension*)
- Bleeding events may very commonly occur, especially if you are also taking blood-thinning medicines (*anticoagulants*)
- Frequency not known: bronchospasm (sudden constriction of the muscles in the walls of the small airways) and wheezing (see also section 2 “Take special care with Ventavis”)

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Below we list other possible side effects by how likely they are:

- **Very common side effects**
  - widening of the blood vessels (*vasodilatation*). Symptoms can be flushing or reddening of the face.
  - chest discomfort / chest pain
  - increase in coughing
  - headache
  - nausea
  - pain in jaw/spasm of the jaw muscles (*trismus*)

- **Common effects**
  - breathing difficulties (*dyspnoea*)
  - dizziness
  - vomiting
  - diarrhoea,
  - pain when swallowing (pharyngolaryngeal irritation and throat irritation)
  - mouth and tongue irritation
  - rash

**Side effects for which frequency is not known**

- Hypersensitivity (i.e. allergy)
- Disturbed sense of taste (*dysguesia*)

- **Other possible effects**

  - Swelling, mainly of the ankles and legs, due to fluid retention (*peripheral oedema*) is a very common symptom of the illness itself but can also occur during treatment with Ventavis.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, **tell your doctor or pharmacist**.

5. **HOW TO STORE VENTAVIS**

Keep out of the reach and sight of children.

Do not use Ventavis after the expiry date which is stated on the pack.

There are no special storage instructions.

Discard any Ventavis solution that you do not use in inhalation session.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
6. FURTHER INFORMATION

What Ventavis contains:

- **The active substance** is iloprost.
  
  1 ml solution contains 10 micrograms iloprost (as iloprost trometamol).
  Each ampoule with 1 ml contains 10 micrograms iloprost.
  Each ampoule with 2 ml contains 20 micrograms iloprost.

- **The other ingredients** are trometamol, ethanol 96%, sodium chloride, hydrochloric acid for pH adjustment, and water for injections.

Ventavis is provided in colourless ampoules (type I glass), containing either 1 ml or 2 ml nebuliser solution.

What Ventavis looks like and content of the pack:

Ventavis is a clear, colourless nebuliser solution for inhalation.

Ventavis is available in packs containing:

- 30, 90, 100, or 300 ampoules with 2 ml for the use with HaloLite, Prodose and Venta-Neb. The ampoules containing 2 ml show two coloured rings (white – pink).
- or 30 or 168 ampoules with 1 ml for use with the I-Neb nebuliser. The ampoules containing 1 ml show two coloured rings (white - yellow).

Not all pack-sizes may be marketed.

**Marketing Authorisation Holder:**
Bayer Schering Pharma AG, D-13342 Berlin, Germany

**Manufacturer:**
Berlimed S.A., Poligono Industrial Santa Rosa s/n, 28806 Alcalá de Henares, Madrid, Spain
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

<table>
<thead>
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<th>Address</th>
<th>Contact Details</th>
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<tbody>
<tr>
<td>België/Belgique/Belgien</td>
<td>Bayer SA-NV</td>
<td>Tél/Tel: +32-(0)2-535 63 11</td>
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<tr>
<td>България</td>
<td>Bayer България ЕООД</td>
<td>тел. +359-(0)2-81 401 01</td>
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<tr>
<td>Česká republika</td>
<td>Bayer s.r.o.</td>
<td>Tel: +420-266 101 111</td>
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<td>Danmark</td>
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<td>Deutschland</td>
<td>Bayer Vital GmbH</td>
<td>Tel: +49-(0)214-30 513 48</td>
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<tr>
<td>Eesti</td>
<td>Bayer OÜ</td>
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<td>Elláda</td>
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<tr>
<td>France</td>
<td>Bayer Santé</td>
<td>Tél.: +33-(0)3-28 16 34 00</td>
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<tr>
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<td>Bayer Limited</td>
<td>Tel: + 353-(0)1-2999 313</td>
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<td>Ísland</td>
<td>Icepharma hf.</td>
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<td>Tél/Tel: +32-(0)2-535 63 11</td>
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</tbody>
</table>
This leaflet was last approved in

This medicine has been authorised under “exceptional circumstances”. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The European Medicines Agency (EMA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

The following information is intended for medical or healthcare professionals only:

Instructions for use and handling

Two compressed air nebuliser systems, HaloLite and Prodose, have been shown to be suitable nebulisers for the administration of Ventavis. 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.

<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated Inhalation time (frequency of 15 breaths per minute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HaloLite</td>
<td>2.5 micrograms</td>
<td>4 to 5 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>8 to 10 min</td>
</tr>
<tr>
<td>Prodose</td>
<td>2.5 micrograms</td>
<td>4 to 5 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>8 to 10 min</td>
</tr>
</tbody>
</table>

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.

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 Venta-Neb nebuliser.

<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated Inhalation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>VentaNeb</td>
<td>2.5 micrograms</td>
<td>8 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>4 min</td>
</tr>
</tbody>
</table>

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, showing two coloured rings (white - yellow), will be transferred into the appropriate nebuliser medication chamber immediately before use.

<table>
<thead>
<tr>
<th>Device</th>
<th>Dose of iloprost at mouthpiece</th>
<th>Estimated Inhalation time</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-Neb AAD</td>
<td>2.5 micrograms</td>
<td>6.5 min</td>
</tr>
<tr>
<td></td>
<td>5 micrograms</td>
<td>3.2 min</td>
</tr>
</tbody>
</table>

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 stabilized on one nebuliser should not switch to another nebuliser without supervision by the treating physician.

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.