

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ventavis 10 microgram/ml nebuliser solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Nebuliser solution.

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Ventavis is intended for inhalation use by nebulisation.

Adults

- Dose per inhalation session:

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

Two compressed air nebuliser systems, HaloLite and Prodose, have been shown to be suitable nebulisers for the administration of Ventavis. With both systems the mass median aerodynamic diameter of the aerosol droplet (MMAD) with iloprost was between 2.6 and 2.7 μm . For each inhalation session the content of one 2-ml ampoule of Ventavis will be transferred into the nebuliser medication chamber immediately before use. HaloLite and Prodose are dosimetric systems. They stop automatically after the pre-set dose has been delivered. The inhalation time depends on the patient's breathing pattern.

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

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

The efficacy and tolerability of inhaled iloprost when administered with other nebulising systems, which provide different nebulisation characteristics of iloprost solution, have not been established.

- Daily dose:

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

- Duration of treatment:

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

Patients with hepatic impairment

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

To avoid undesired accumulation over the day, special caution has to be exercised with these patients during initial dose titration. Initially, doses of 2.5 µg should be administered with dosing intervals of at least 3 hours (corresponds to administration of max. 6 times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a further increase in the dose up to 5.0 µg is indicated, again dosing intervals of at least 3 hours should be chosen initially and shortened according to individual tolerability. A further undesired accumulation of the medicinal product following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

Patients with renal impairment

There is no need for dose adaptation in patients with a creatinine clearance > 30 ml/min (as determined from serum creatinine using the Cockcroft and Gault formula). Patients with a creatinine clearance of ≤ 30 ml/min were not investigated in the clinical trials.

Children and adolescents (below 18 years of age)

Currently no experience in children and adolescents is available.

4.3 Contraindications

Hypersensitivity to iloprost or to any of the excipients.

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

Severe coronary heart disease or unstable angina; myocardial infarction within the last six months; decompensated cardiac failure if not under close medical supervision; severe arrhythmias; cerebrovascular events (e.g. transient ischaemic attack, stroke) within the last 3 months.

Pulmonary hypertension due to venous occlusive disease.

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

Pregnancy, lactation.

4.4 Special warnings and special precautions for use

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

The pulmonary vasodilatory effect of inhaled iloprost is of short duration (one to two hours). Patients who experience syncope in association with pulmonary hypertension should avoid any exceptional straining, for example during physical exertion. Before physical exertion it might be useful to inhale. The occurrence of a nocturnal or exertional syncope reflects therapeutic gaps and/or insufficient efficiency, and the need to adapt and/or change the therapy should be considered (see section 4.8).

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

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

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

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

Iloprost elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis (see section 5.2). A cautious initial dose titration using dosing intervals of at least 3 hours is recommended (see section 4.2).

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Iloprost may increase the effect of vasodilators and antihypertensive agents.

Iloprost can inhibit platelet function and its use with anticoagulants (such as heparin, coumarin-type anticoagulants) or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, ticlopidine, clopidogrel and glycoprotein IIb/IIIa antagonists: abciximab, eptifibatid and tirofiban) may increase the risk of bleeding. A careful monitoring of the patients taking anticoagulants according to common medical practice is recommended. The concomitant use of other platelet inhibitors should be avoided in patients taking anticoagulants.

Intravenous infusion of iloprost has no effect either on the pharmacokinetics of multiple oral doses of digoxin or on the pharmacokinetics of co-administered tissue plasminogen activator (t-PA) in patients. Although, clinical studies have not been conducted, *in vitro* studies investigating the inhibitory potential of iloprost on the activity of cytochrome P450 enzymes revealed that no relevant inhibition of drug metabolism via these enzymes by iloprost have to be expected.

4.6 Pregnancy and lactation

- **Pregnancy**

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

- **Lactation**

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

Cardiovascular disorders

Very common: vasodilatation, hypotension

Common: syncope

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 (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Very common: increased cough

Nervous system disorders

Common: headache

Musculoskeletal disorders

Common: trismus

Bleeding events (mostly haematoma) were common as expected in this patient population with a high proportion of patients taking anticoagulant co-medication. The frequency of bleeding events did not differ between iloprost and placebo-treated patients.

4.9 Overdose

- Symptoms

No case of overdose has been reported. Hypotensive/vasovagal reaction might be anticipated as well as headache, flushing, nausea, vomiting, and diarrhoea.

- 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

Pharmacotherapeutic group: Platelet aggregation inhibitors excluding heparin, ATC code: B01A C

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.

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 µg (range

12.5 to 45 µg/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.

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.

- 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 C_{max} 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

Iloprost is not a gene mutagen in bacterial and mammalian cells *in vitro* and is not clastogenic in human lymphocytes up to cytotoxic concentrations and in the micronucleus test *in vivo*.

No tumorigenic potential of iloprost could be demonstrated 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 the foetuses/pups up to the highest tested dose.

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

No special precautions for storage.

6.5 Nature and contents of container

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

Packages containing 30, 100 and 300 ampoules.

6.6 Instructions for use and handling

For each inhalation session the contents of one opened ampoule of Ventavis has to be transferred into the nebuliser medication chamber immediately before use. After each inhalation session, any solution remaining in the nebuliser should be discarded.

7. MARKETING AUTHORISATION HOLDER

Schering AG, D-13342 Berlin, Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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 AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Schering AG, Müllerstraße 170 – 178, 13342 Berlin, Germany

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

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OF THE MARKETING AUTHORISATION

• **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

• **OTHER CONDITIONS**

The holder of this marketing authorisation must inform the European Commission about the marketing plans for the medicinal product authorised by this decision.

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION 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:

1. The applicant will seek Protocol Assistance within 4 months after the final CPMP opinion to discuss an adequate protocol to gather further data on longer-term safety and efficacy of Ventavis (iloprost). Progress reports will be provided together with the submission of the PSURs. The first patient will be enrolled within 9 months after adoption of the Protocol Assistance. A final report will be provided within 6 months after last patient completed.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON / 30 AMPOULES

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

3. LIST OF 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

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

There are no special storage instructions

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

Schering AG, D-13342 Berlin, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON / 100 AMPOULES

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

3. LIST OF EXCIPIENTS

trometamol, ethanol 96 %,
sodium chloride, hydrochloric acid for pH adjustment,
water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution
100 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

There are no special storage instructions

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

Schering AG, D-13342 Berlin, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

OUTER CARTON / 300 AMPOULES

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

3. LIST OF EXCIPIENTS

trometamol, ethanol 96 %,
sodium chloride, hydrochloric acid for pH adjustment,
water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser solution
300 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

There are no special storage instructions

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

Schering AG, D-13342 Berlin, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/0/00/000/000

13. MANUFACTURER'S BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Ampoule

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

Ventavis 10 microgram/ml
Nebuliser solution
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

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Please be sure to read all of this leaflet carefully before you start using this medicine.

- Please keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

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. STORING VENTAVIS**
- 6. FURTHER INFORMATION**

Ventavis 10 Microgram/ml nebuliser solution
Iloprost

- **The active substance** is iloprost (as iloprost trometamol).
1 ml solution contains 10 micrograms iloprost (as iloprost trometamol). Each 2-ml ampoule contains 20 micrograms iloprost (as iloprost trometamol).
- **The other ingredients** are trometamol, ethanol 96%, sodium chloride, hydrochloric acid for pH adjustment, and water for injections.

Marketing Authorisation Holder

Schering AG, D-13342 Berlin, Germany

Manufacturer

Schering AG, D-13342 Berlin, Germany or

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

1. WHAT VENTAVIS IS AND WHAT IT IS USED FOR

Ventavis is a nebuliser solution. This clear, colourless solution is changed into an aerosol mist by a special machine called a nebuliser. Breathing in the mist carries Ventavis to the lungs, where it can work most effectively in the artery between heart and lungs.

Packaging

Each ampoule contains 2 ml of nebuliser solution and provides adequate quantity for one inhalation session. A pack of Ventavis may contain 30, 100 or 300 ampoules.

What Ventavis is

Ventavis 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 arteries.

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.

Ventavis tends to lower blood pressure within the pulmonary artery, by improving blood flow. This means less work for the heart. Improved blood flow leads to an improved supply of oxygen to the body and reduced strain on the heart. The heart can function more effectively.

2. BEFORE YOU USE VENTAVIS

Do not use Ventavis

If you think any of the following may apply to you, **please tell your doctor:**

- **If you have an allergy** to iloprost or any of the other ingredients of Ventavis (see above).
- **If you are at risk of bleeding**— for example, active stomach ulcers, injuries, or other bleeding
- **If you have a significant build-up of fluid in the lungs**, with difficulty in breathing
- **If your disease is due to a blocked or narrow vein** rather than a blocked or narrow artery
- **If you have had a stroke within the last 3 months**, or any other interruption of blood supply to the brain
- **If you have a heart problem**, for example:
 - a heart attack within the last six months
 - severe changes in heart rate
 - you sometimes have chest pain
 - poor blood flow to the muscles of the heart (*coronary heart disease*)
 - any disease of the heart which is not being treated or not under close medical observation
 - a heart defect has been diagnosed, such as a faulty heart valve that causes the heart to work poorly.

Ventavis is not for pregnant women

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

Ventavis is not for women who are breast-feeding

Stop breast-feeding when you start Ventavis 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.

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.

Children and adolescents

Ventavis has not yet been tested in children and adolescents.

Take special care with Ventavis

If your blood pressure is too low (less than 85 mmHg) you should not start the therapy with Ventavis.

You will need special medical observation in some cases:

- In general, you will need to **take special care to try and avoid fainting** or other effects of low blood pressure, such as dizziness:
 - Stand up slowly when you get out of chairs or bed. You will help your body get used to the change in position and blood pressure
 - 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're still lying down
 - Avoid any exceptional straining, for example physical exertion; it might be useful to inhale Ventavis before such physical exertion

- Have someone on standby to watch you, if possible. Warn them to **call a doctor if you faint**. The doctor will give advice on what to do and possibly prescribe treatment
- If fainting episodes get worse because of the underlying disease, tell your doctor. The doctor may consider a change of treatment
- **If you have liver problems**, you may be prescribed a lower dose of Ventavis than for other patients
- **If you have very severe kidney problems**, see your doctor
- **If you have infection of the lungs, severe asthma**, or other lung disease
- **If your overall condition becomes worse**, see your doctor
- **If Ventavis therapy has been stopped**, since symptoms might worsen.

Your ability to drive or use machines

Ventavis brings down 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 of low blood pressure.

Are you taking any other medicines?

Please tell your doctor about all other medicines you might be taking or have recently taken, including any that you buy without a prescription. Ventavis and certain other medicines may influence each other in the way they work in your body. Be specially careful to mention any of these:

- Medicines used to treat high blood pressure or heart disease
- Medicines which inhibit blood clotting (this includes acetylsalicylic acid a substance present in many medicines that lower fever and relieve pain, as well as others)

Your doctor or pharmacist has more information on medicines to be careful with or avoid when using Ventavis, so always tell them if you are taking other medicines.

3. HOW TO USE VENTAVIS

Ventavis nebuliser solution is inhaled using the nebulisers your doctor prescribed (either the HaloLite or the Prodose system). The nebuliser turns Ventavis solution into a mist which you breathe in through your mouth.

Just before you start to inhale, break open the glass container and transfer the complete contents into the nebuliser medication chamber.

You should run the inhalation cycle twice if you require a high dose (5 µg) and once if you require a low dose (2.5 µg). Independent of the dose the filling volume is always the contents of one glass container.

Always take Ventavis exactly as your doctor has told you. Follow carefully any extra instructions that come with the nebuliser. Check with your doctor or pharmacist if you are unsure. Ask your doctor to have someone help you become thoroughly familiar with the use of the nebuliser.

Ventavis solution that you do not use in one inhalation session has to be thrown away.

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 drinking accidentally occurs, drink plenty of water and talk to a doctor. Drinking Ventavis could also lead to a temporary overdose – see “**What to do if you take more Ventavis than you should**”.

How much to take

The dose of Ventavis that is right for you depends on your individual condition and will be worked out by your doctor.

Most people will have 6 to 9 inhalation sessions spread out through each day. One inhalation session will usually last about 4 to 10 minutes depending on the prescribed dose. In case of liver problems, your doctor will introduce you to Ventavis gradually and possibly prescribe fewer daily inhalations.

If you have the impression that the effect of Ventavis is too strong or too weak, **talk to your doctor or pharmacist**.

What to do if you take more Ventavis than you should

You may get a severe headache, flushing (reddening of the face), nausea, vomiting and/or diarrhoea, and this may even lead to a severe decrease in blood pressure, causing dizziness or fainting. If this happens:

- Stop the inhalation session
- Talk to your doctor

See also section 2, Take special care with Ventavis, for advice on what you have to do if you have low blood pressure or fainting episodes.

What to do if you miss a dose

Your doctor will discuss with you when to take Ventavis. If you miss a dose, do not worry. Please ask your doctor what you should do.

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.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ventavis can have side effects, and most people using it are likely to have some of these. Below we list possible side effects by how likely they are.

Very common effects

10 or more in every 100 people are likely to get these.

- Flushing, or reddening of the face, caused by widening of the blood vessels
- Increase in coughing
- Low blood pressure (hypotension).

Common effects

Between 1 and 10 in every 100 people are likely to get these.

- Headaches
- Spasm of the jaw muscles (difficulty in opening the mouth)
- 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 stop this.**

Other possible effects

If you are also taking blood-thinning medicines (anticoagulants), minor bleeding events are likely to occur.

If you are worried about any of these effects or suffer any other effects not mentioned here, or if your overall condition worsens, **tell your doctor or pharmacist.**

5. STORING VENTAVIS

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label (printed after the letters EXP).

There are no special storage instructions.

Please turn over →

6. FURTHER INFORMATION

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last approved on {date}

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 2-ml ampoule of Ventavis will be transferred into the nebuliser medication chamber immediately before use. HaloLite and Prodose are dosimetric systems. They stop automatically after the pre-set dose has been delivered. The inhalation time depends on the patient's breathing pattern.

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

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

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.