

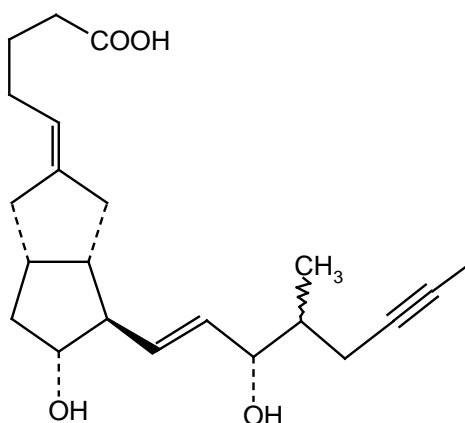
# Data Sheet

VENTAVIS®

Iloprost 20 µg/2 mL

## NAME OF THE MEDICINE

Iloprost 20 µg/2 mL nebuliser solution



Substance Code ZK 36374

CHEMICAL NAME: (E)-(3aS,4R,5R,6aS)-Hexahydro-5-hydroxy-4((E)-(3S,4RS)-3-hydroxy-4methyl-1octen-6-ynyl)- $\Delta^{2(1H)\delta^5}$ -pentalenevaleric acid.

MOLECULAR FORMULA: C<sub>22</sub>H<sub>32</sub>O<sub>4</sub>

MOLECULAR WEIGHT: 360.48

CAS NUMBER: 73873-87-7

## DESCRIPTION

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

## PHARMACOLOGY

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

After inhalation of Ventavis, direct vasodilatation of the pulmonary arterial bed occurred with consecutive significant improvement of pulmonary artery pressure, pulmonary vascular resistance and cardiac output as well as mixed venous oxygen saturation. Effects on systemic vascular resistance and systemic arterial pressure were minor. Pharmacokinetics

- Absorption

When iloprost is administered via inhalation in patients with pulmonary hypertension (iloprost dose at the mouthpiece: 5 µg), peak serum levels of 100 to 200 pg/mL were observed at the end of inhalation. 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 pg/mL).

- Distribution

No studies were performed following inhalation of Ventavis.

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 pg/mL and amounts to approximately 60%, of which 75% is due to albumin binding.

- Metabolism

No studies to investigate the metabolism of iloprost were performed following inhalation of Ventavis.

*In vitro* studies suggest, however, that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.

After intravenous administration, iloprost is extensively metabolised via  $\beta$ -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. Tetranor-iloprost is pharmacologically inactive as shown in animal experiments.

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

- Elimination

No studies were performed following inhalation of Ventavis.

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  $^3\text{H}$ -iloprost in healthy subjects. Following intravenous infusion, the recovery of total radioactivity is 81%, and the respective recoveries in urine and faeces are 68% and 12%. The metabolites are eliminated from plasma and with urine in 2 phases, for which half-lives of about 2 and 5 hours (plasma) and 2 and 18 hours (urine) have been calculated.

- Characteristics in patients

Renal dysfunction:

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

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

**Table 1. Pharmacokinetics of intravenous iloprost in patients with renal dysfunction**

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

$\alpha$  and  $\beta$  phases refer to biphasic disposition.

In a study with intravenous infusion of iloprost, patients with end stage renal failure undergoing intermittent dialysis treatment were shown to have a significantly lower clearance (mean CL = 5 ± 2 mL/minute/kg) than that observed in patients with renal failure not undergoing intermittent dialysis treatment (mean CL = 18 ± 2 mL/minute/kg). The half lives were similar in the two groups.

Hepatic dysfunction:

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

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

Subjects	Cirrhotic	Normal (historical control)		Normal (historical control)
Number of subjects	8	6		8
Age	56±9 years	30±8 years		59±5years
Dose (ng/kg/min)	1	1	3	2
C <sub>ss</sub> (pg/mL)	93	46	135	81
Clearance (total) (mL/min/kg)	10±5	21±3	20±5	24±9
t <sub>1/2</sub> (min)	28±24	20±7	26±7	31±10

Because iloprost is extensively metabolised by the liver, the plasma levels of the drug are influenced by changes in hepatic function. In an intravenous study, results were obtained involving 8 patients suffering from liver cirrhosis. The mean clearance of iloprost in the study was estimated to be 10 mL/minute/kg. The results indicate that clearance of iloprost was reduced by 50% in the group of cirrhotic patients compared to the historical control groups. There is no effect on t<sub>1/2</sub>.

Age and gender:

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

## **CLINICAL TRIALS**

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

### **Phase II Study (A00794)**

This was an open-label randomised phase II multicentre study which included a three month controlled phase (with either inhaled iloprost added to conventional therapy or conventional therapy alone) before patients went on to an open-label, long term therapy with inhaled iloprost for up to two years.

Patients with New York Heart Association (NYHA) functional class II, III or IV were included with a mean pulmonary arterial pressure (mPAP) of about 30 or 40 mmHg, for primary pulmonary hypertension (PPH) or secondary pulmonary hypertension (SPH) respectively.

Thirty patients were randomised to the iloprost group and 33 to the control group. Fifteen patients prematurely discontinued study medication (8 iloprost and 7 control patients). After the end of the three month phase, 52 patients entered the long-term treatment phase with inhaled iloprost for up to 24 months.

During the randomised phase the median nominal daily iloprost dose was 100 µg (50 µg to 150 µg). During the long term study phase the median range daily dose was 100 µg (range 50 µg to 200 µg).

The following results were obtained during the three month randomised phase:

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

The following interim results were obtained from 9-12 months of the follow up phase:

- Patients remained stable or improved (NYHA class and Mahler dyspnoea index).
- Pre inhalation values of haemodynamics and gas exchange remained stable compared to baseline.
- Peak haemodynamic effect improved significantly.
- Acute response to iloprost inhalation maintained after long term treatment. No development of drug effect tolerance.

### Phase III Study (A02997)

This was a multicentre double-blind randomised placebo controlled efficacy and safety study of 12 weeks duration. The study included 203 patients belonging to class III or IV NYHA functional class. The median inhaled iloprost daily dose was 30 µg divided into 6 inhalations (range 12.5 µg to 45 µg). There was no tolerance development.

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

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

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

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

Death and defined criteria of deterioration: One patient in the iloprost group and 4 patients in the placebo group died ( $p=0.369$ ) during the 12 week observation period. One patient from the iloprost group died after discontinuing the study. During the follow up period (up to week 16), 2 further patients originally randomised to the iloprost group and 3 placebo patients died. There was no statistically significant difference in the rate of death or deterioration in patients taking iloprost compared to placebo.

Mahler dyspnoea index: Iloprost showed a significantly better improvement compared to placebo ( $p = 0.015$ ).

The overall incidence of side effects reported up to 12 weeks were comparable between the treatment groups for both the Phase I and Phase II study.

**Table 3. Overview of secondary endpoints** <sup>(3), (6)</sup>

	Iloprost n = 101	Placebo n = 102	Treatment Effect p-value
Improvement in NYHA class** n (%)	25 (24.8%)	13 (12.7%)	<u>0.032</u> <sup>(4)</sup>
Improvement of WD of 10% vs. baseline** n (%)	38 (37.6%)	26 (25.5%)	<u>NS</u> <sup>(7)</sup>
Walking distance – change from baseline*# [m] mean SD median change	n = 95 22.2 ± 71.4 20.0	n = 85 -3.3 ± 74.2 0.0	<u>0.032</u> <sup>(1)</sup>
Perceived exertion (RPE) scale*# absolute change to baseline mean SD	n = 95 -0.38 ± 2.7	n = 84 0.04 ± 2.9	<u>NS</u> <sup>(7)</sup>
Deterioration n (%)	5 (4.9%)	9 (8.8%)	<u>NS</u> <sup>(7)</sup>
Mortality until week 12 n (%)	1 (1.0%)	4 (3.9%)	<u>NS</u> <sup>(7)</sup>
Need for transplantation* patients newly scheduled n (%)	2 (2.0%)	4 (3.9%)	<u>NS</u> <sup>(7)</sup>

MDI focal score – change to baseline* mean SD	n = 96 0.448 ± 1.691	n = 86 0.174 ± 1.365	<u>NS</u> <sup>(7)</sup>
MDI transition score* mean SD	n = 96 1.42 ± 2.6	n = 86 0.30 ± 2.5	<u>0.015</u> <sup>(2)</sup>
EQ-VAS – change to baseline* mean SD	n = 95 5.43 ± 17.32	n = 82 -1.77 ± 18.95	<u>0.016</u> <sup>(5)</sup>

\* Findings based on observed cases only.

\*\* Component of the primary endpoint.

# Values obtained at week 12 after inhalation.

(1) Non-parametric analysis of covariance with baseline value as covariate.

(2) Two-sided Kruskal-Wallis test on absolute values.

(3) Fisher's exact test.

(4) Stratified Mantel-Haenszel test.

(5) Analysis of covariance.

(6) One-way ANOVA model.

(7) NS = not significant

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

## INDICATIONS

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

## CONTRAINDICATIONS

Hypersensitivity to iloprost or to any of the excipients.

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

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

Pulmonary hypertension due to venous occlusive disease.

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

## PRECAUTIONS

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

## **Risk of syncope**

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

The pulmonary vasodilatory effect of inhaled iloprost is of short duration (one or two hours).

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

Physicians should be alert to the presence of concomitant conditions or medicines that might increase the risk of syncope (see Interactions with other medicines). Syncope is also a common symptom of the disease itself. If syncope occurs on rising, it may be helpful to take the first dose of the day on waking, while still recumbent. 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 Ventavis. The increased occurrence of syncopes can reflect therapeutic gaps and/or deterioration of the disease.

## **Bronchospasm**

Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperreactivity (see ADVERSE EFFECTS). The benefit of Ventavis has not been established in patients with concomitant Chronic Obstructive Pulmonary Disease (COPD) and severe asthma. Patients with concomitant acute pulmonary infections, chronic obstructive pulmonary disease, and severe asthma should be carefully monitored.

## **Pulmonary venous hypertension**

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

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

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.

## **Patients with hepatic and renal impairment**

The need to adapt and/or change the therapy should be considered (see ADVERSE EFFECTS). Based on data with intravenously administered iloprost the elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis and a dose reduction may be considered. A cautious initial dose titration using dosing intervals of 3 – 4 hours is recommended (see DOSAGE AND ADMINISTRATION and Pharmacokinetics).

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

## **Effects on fertility**

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

## **Use in Pregnancy**

Use in Pregnancy (Category B3)

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

There are no adequate data from the use of Ventavis in pregnant women. Animal studies have shown reproductive toxicity. In embryo- and fetotoxicity studies in rats, continuous IV infusion of iloprost increased skeletal anomalies at 0.01- to 1 mg/kg/day (incomplete ossification and shortened digits of the forepaws) and embryofetal resorption at 1 mg/kg/day. These alterations are not considered as teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to haemodynamic alterations in the fetoplacental unit. No disturbance of postnatal development and reproductive performance was seen in the offspring that were raised, indicating that the observed retardation in rats was compensated during the postnatal development.

Increased embryofetal resorption and/or incomplete ossification, but not shortened digits, were also observed in rats treated with 34.4 mg/kg/day iloprost by oral gavage (ca 600 times the clinical exposure based on AUC) or in rabbits treated with 0.5 mg/kg/day iloprost by continuous IV infusion or 5.6 mg/kg/day by oral gavage (ca 300 times the clinical exposure based on AUC). There was no evidence of embryofetal toxicity in a monkey study at up to 40 µg/kg/day (9 fetuses examined at this dose) by continuous IV infusion (60 times the anticipated clinical exposure based on AUC). In comparable embryotoxicity studies in rabbits and monkeys no such digit anomalies or other gross-structural anomalies were observed even after considerably higher dose levels which exceeded the human dose multiple times. The gestation time in rats was also prolonged slightly at 1 mg/kg/day by continuous IV infusion.

The potential risk to humans is not known. Therefore women of child bearing potential should use effective contraceptive measures during treatment with Ventavis .If a pregnancy occurs, Ventavis should only be used following careful risk-benefit evaluation.

## **Use in Lactation**

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

## **Carcinogenicity and mutagenicity**

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

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

### **Interactions with other medicines**

Iloprost may increase the antihypertensive effect of vasodilating and antihypertensive agents (see PRECAUTIONS). Caution is recommended in case of co-administration of Ventavis with vasodilating or antihypertensive agents as dose adjustment might be required.

Because iloprost inhibits platelet function, its use with anticoagulants (such as heparin, coumarin-type anticoagulants), or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, phosphodiesterase inhibitors and nitro vasodilators) may increase the risk of bleeding (see ADVERSE EFFECTS). If bleeding occurs, iloprost administration should be stopped. Careful monitoring of the patients taking anticoagulants or other inhibitors of platelet aggregation according to common medical practice is recommended.

Oral premedication with acetylsalicylic acid up to 300 mg per day over a period of 8 days had no impact on the pharmacokinetics of iloprost. The results of human studies show that iloprost infusions do not affect the pharmacokinetics of multiple oral doses of digoxin in patients and iloprost has no impact on the pharmacokinetics of co-administered tissue-type plasminogen activator (t-PA). In an animal study, it was found that iloprost may result in a reduction in t-PA steady-state plasma concentration.

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

Although, clinical studies have not been conducted, *in vitro* studies investigating the inhibitory potential of iloprost on the activity of cytochrome P450 enzymes revealed that no relevant inhibition of drug metabolism via these enzymes by iloprost have to be expected.

### **Effects on ability to drive and use machines**

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

### **ADVERSE EFFECTS**

In addition to local effects resulting from administration of iloprost by inhalation such as cough, adverse drug reactions (ADRs) with iloprost are related to the pharmacological properties of prostaglandins. The most frequently observed ADRs ( $\geq 20\%$ ) in clinical trials include vasodilatation, headache and cough. The most serious adverse reactions were hypotension, bleeding events, and bronchospasm.

ADRs reported below are based on pooled clinical trial data from phase II and III clinical trials involving 131 patients taking the medication.

The ADRs observed with Ventavis are represented in the table below. They are classified according to System Organ Class (MedDRA version 14.0). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

ADRs from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention:

Very common  $\geq 1/10$

Common  $\geq 1/100$  to  $< 1/10$

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

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

**Table 4. Adverse Drug Reactions reported based on clinical trial data**

<b>System Organ Class (MedDRA)</b>	<b>Very common (<math>\geq 1/10</math>)</b>	<b>Common (<math>\geq 1/100</math> to <math>&lt; 1/10</math>)</b>	<b>Not known</b>
Blood and lymphatic system disorders	Bleeding events <sup>#§</sup>		Thrombocytopenia
Immune system disorders			Hypersensitivity
Nervous system disorders	Headache	Dizziness	
Vascular disorders	Vasodilation	Hypotension <sup>#</sup> Syncope <sup>*</sup>	
Respiratory, thoracic and mediastinal disorders	Chest pain Cough	Dyspnoea Pharyngolaryngeal pain Throat irritations	Bronchospasm <sup>#</sup> Wheezing
Gastrointestinal disorders	Nausea	Diarrhoea Vomiting Mouth and tongue irritation including pain	Dysgeusia
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal and connective tissue disorders	Pain in jaw/trismus	Back pain	

<sup>#</sup>life-threatening and/or fatal cases have been reported

<sup>§</sup>Bleeding events (mostly epistaxis and haemoptysis) were very common as expected in this patient population with a high proportion of patients taking anticoagulant comedication. The risk of bleeding may be increased in patients when inhibitors of platelet aggregation or anticoagulants are given concomitantly (see Interactions with other medicines).

<sup>\*</sup>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.

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.

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

## DOSAGE AND ADMINISTRATION

The solution is administered with a suitable inhalation device (nebuliser) as recommended in Instructions for use/ handling. Previous therapy should be continued and adjusted to individual needs (see Interactions with other medicines). In order for the correct dose of iloprost to be delivered to the patient a suitable nebuliser must be used. The HaloLite nebuliser described in the Clinical trial section is not currently available in New Zealand. Clinical data on the use of other similar nebulisers with Ventavis is not available. See Use with nebulisers, for further information.

### Recommended dose:

- Adults

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

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

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

### *Duration of treatment*

#### Long term treatment

- Patients with hepatic impairment

Iloprost elimination is reduced in patients with hepatic dysfunction. Caution should be used during therapy in patients with Child-Pugh class B or more severe hepatic impairment. It should also be used with caution in patients with mild to moderate hepatic impairment.

To avoid undesired accumulation over the day, special caution has to be exercised with these patients during initial dose titration. Initially, doses of 2.5 µg should be administered with dosing intervals of 3 – 4 hours (corresponds to administration of max. 6 times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a further increase in the dose up to 5.0 µg is indicated, again dosing intervals of 3 – 4 hours should be chosen initially and shortened according to individual tolerability. An accumulation of iloprost following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

- Patients with renal impairment

There is no need for dose adaptation in patients with a creatinine clearance >30 mL/min (as determined from serum creatinine using the Cockcroft and Gault formula). Patients with a creatinine clearance ≤30 mL/min were not investigated in the clinical trials. Based on data with intravenously administered iloprost the elimination is reduced in patients with renal

failure requiring dialysis. For dosing recommendations, see Patients with hepatic impairment.

- Paediatric patients/ Children and adolescents (below 18 years of age)

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

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

### **Instructions for use/handling**

For each inhalation session a new ampoule of Ventavis should be used. The content of the opened ampoule has to be completely transferred into the nebuliser chamber immediately before use.

Nebuliser solution not used in one inhalation session has to be discarded. In addition, instructions for hygiene and cleaning of the nebulisers provided by the device manufacturers should be followed carefully.

Use with nebulisers:

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

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

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

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

### **Incompatibilities**

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

### **OVERDOSAGE**

- Symptoms

No case of overdose has been reported. Hypotensive 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 also be possible.

- Therapy

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

## **PRESENTATION AND STORAGE CONDITIONS**

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

Each ampoule contains 20 µg iloprost (as trometamol).

Store below 30°C.

2 mL x 30 ampoules

2 mL x 100 ampoules

2 mL x 300 ampoules

Not all pack sizes may be marketed.

### **Shelf life**

See the pack for expiry information

## **NAME AND ADDRESS OF THE SPONSOR**

Bayer New Zealand Limited

3 Argus Place

Hillcrest

North Shore

Auckland 0627

New Zealand

Free Phone: 0800 233 988

## **MEDICINE CLASSIFICATION**

Prescription Medicine

## **DATE OF PREPARATION**

17 October 2011

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