NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Ventavis® 20 microgram/2 mL nebuliser solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ventavis 10 microgram/mL nebuliser solution

1 mL solution contains 10 microgram iloprost (as iloprost trometamol).
Each ampoule with 2 mL solution contains 20 microgram iloprost.

Excipient with known effect

Ventavis 10 microgram/mL:
Each mL contains 0.81 mg ethanol 96% (equivalent to 0.75 mg ethanol)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nebuliser solution.

Ventavis 10 microgram/mL nebuliser solution

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Dose and method of administration

Dose

Adults

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

The dose per inhalation session should be administered 6 to 9 times per day 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. 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.

Special populations

Renal impairment

There is no need for dose adaptation in patients with a creatinine clearance >30 mL/min (as determined from serum creatinine using the Cockroft and Gault formula). Patients with a creatinine clearance ≤30 mL/min were not investigated in the clinical trials. Based on data with intravenously administered iloprost the elimination is reduced in patients with renal failure requiring dialysis. For dosing recommendations, see Hepatic impairment.

Hepatic impairment

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

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

Paediatric population

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

Method of administration

The solution is administered with a suitable inhalation device (nebuliser) as recommended in section 6.6. Previous therapy should be continued and adjusted to individual needs (see section 4.5). 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 section 5.1 is not currently available in New Zealand. Clinical data on the use of other similar nebulisers with Ventavis is not available. See section 6.6 for further information.

4.3 Contraindications

Hypersensitivity to iloprost or to any of the excipients listed in section 6.1.

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.

4.4 Special warnings and precautions for use

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

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

Risk of syncope

Physicians should be alert to the presence of concomitant conditions or medicines that might increase the risk of syncope (see section 4.5). Syncope is also a common symptom of the disease itself. 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 pulmonary vasodilatory effect of inhaled iloprost is of short duration (one or two hours).The increased occurrence of syncopes can reflect therapeutic gaps and/or deterioration of the disease. The need to adapt and/or change the therapy should be considered. If syncope occurs on rising, it may be helpful to take the first dose of the day on waking, while still recumbent.

Hypotension

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

Bronchospasm

Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperreactivity (see section 4.8). 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 section 4.8). 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 section 4.2 and section 5.2).

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

4.5 Interaction with other medicines and other form of interaction

Iloprost may increase the antihypertensive effect of vasodilating and antihypertensive agents (see section 4.4). Caution is recommended in case of co-administration of Ventavis with vasodilating or antihypertensive agents as dose adjustment might be required.

Because iloprost inhibits platelet function, its use with anticoagulants (such as heparin, coumarin-type anticoagulants), or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, non-selective phosphodiesterase inhibitors [e.g., theophylline, pentoxifylline, dipyridamole], selective phosphodiesterase 3 [PDE3] inhibitors [e.g., milrinone, cilostazol, anagrelide] and nitrovasodilators) may enhance iloprost-mediated platelet inhibition, thereby increasing the risk of bleeding (see section 4.8). 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.

4.6 Fertility, pregnancy and lactation

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 (see section 5.3).

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

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 (see section 5.3).

Effects on fertility

See section 5.3

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

4.8 Undesirable effects

Summary of the safety profile

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 (≥ 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.

Tabulated summary of adverse reactions

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 ≥ 1/10
Common ≥ 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 1. Adverse Drug Reactions reported in patients treated with Ventavis

System Organ Class (MedDRA)	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Not known
Blood and lymphatic system disorders	Bleeding events[#§]		Thrombocytopenia
Immune system disorders			Hypersensitivity
Nervous system disorders	Headache	Dizziness	
Cardiac disorders		Tachycardia Palpitations	
Vascular disorders	Vasodilation	Hypotension[#] Syncope[§]	
Respiratory, thoracic and mediastinal disorders	Chest pain Cough	Dyspnoea Pharyngolaryngeal pain Throat irritations	Bronchospasm[#] Wheezing Nasal congestion
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	
General disorders and administration site conditions	Peripheral oedema[§]		

[#] life-threatening and/or fatal cases have been reported
[§] see section 'Description of selected adverse reactions'.

Description of selected adverse reactions

As expected in patients with pulmonary hypertension, syncopes were common, and did not differ significantly between the treatment groups in frequency (see section 4.4).

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 section 4.5). Fatal cases of cerebral and intracranial haemorrhage have been reported.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting

4.9 Overdose

Cases of overdose were reported. Frequently observed symptoms following overdose are dizziness, headache, flushing, nausea, jaw pain or back pain. Hypotension, an increase of blood pressure, bradycardia or tachycardia, vomiting, diarrhoea and limb pain might also be possible.

Therapy

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin, ATC code: B01AC11

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

Pharmacodynamic effects

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.

Clinical efficacy and safety

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 microgram (50 microgram to 150 microgram). During the long term study phase the median range daily dose was 100 microgram (range 50 microgram to 200 microgram).

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

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

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

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

Phase III Study (A02997)

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

The primary end point was a combined responder criterion consisting of improvement in exercise capacity at 12 weeks by at least 10% versus baseline and improvement by at least

one NYHA class at 12 weeks via baseline and no deterioration of 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 2. Overview of secondary endpoints [3], [6]

	Iloprost n = 101	Placebo n = 102	Treatment Effect p-value
Improvement in NYHA class**n (%)	25 (24.8%)	13 (12.7%)	0.032 [4]
Improvement of WD of 10% vs. baseline** n (%)	38 (37.6%)	26 (25.5%)	NS [7]
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	0.032 [1]
Perceived exertion (RPE) scale*# absolute change to baseline mean SD	n = 95 -0.38 ± 2.7	n = 84 0.04 ± 2.9	NS [7]
Deterioration n (%)	5 (4.9%)	9 (8.8%)	NS [7]
Mortality until week 12 n (%)	1 (1.0%)	4 (3.9%)	NS [7]
Need for transplantation* patients newly scheduled n (%)	2 (2.0%)	4 (3.9%)	NS [7]
MDI focal score – change to baseline* mean SD	n = 96 0.448 ± 1.691	n = 86 0.174 ± 1.365	NS [7]
MDI transition score* mean SD	n = 96 1.42 ± 2.6	n = 86 0.30 ± 2.5	0.015 [2]
EQ-VAS – change to baseline* mean SD	n = 95 5.43 ± 17.32	n = 82 -1.77 ± 18.95	0.016 [5]

* 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.

5.2 Pharmacokinetic properties

Absorption

When iloprost is administered via inhalation in patients with pulmonary hypertension (iloprost dose at the mouthpiece: 5 microgram), mean peak serum concentrations of 100 to

200 pg/mL were observed at the end of inhalation. These concentrations decline with half-lives between approximately 5 and 25 minutes. Within 30 minutes to 1 hour after the end of inhalation, iloprost is not detectable in the central compartment (limit of quantification 25 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.

Biotransformation

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 ß-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}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±0.12 mL/min/kg, and Group 2 included 11 patients with a mean creatinine clearance of 0.16±0.05 mL/min/kg. Iloprost was administered as an intravenous infusion at a rate of 1ng/kg/min for 60 minutes. The mean results are shown in Table 3 below:

Table 3. 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 α-phase (pg.h/mL)	42±17	170±95
T1/2 α-phase (h)	0.06±0.01	0.055±0.005
AUC β-phase (pg.h/mL)	12±14	43±36
T1/2 β-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

α and β 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 4 below:

Table 4. 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_{ss} (pg/mL)	93	46	135	81
Clearance (total) (mL/min/kg)	10±5	21±3	20±5	24±9
$t_{1/2}$ (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 $t_{1/2}$.

Age and gender

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

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenicity

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

Toxicity to reproduction and development

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 microgram/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.

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).

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).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol, ethanol 96%, sodium chloride, hydrochloric acid and 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

Shelf life is 4 years from date of manufacture when stored at or below 30°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

Each ampoule contains 20 microgram iloprost (as trometamol).

2 mL x 30 ampoules
2 mL x 100 ampoules
2 mL x 300 ampoules

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other 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.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Use with nebulisers:

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

Nebulisers suitable for inhalation of iloprost should deliver 2.5 microgram or 5 microgram iloprost at the mouthpiece in a time period of approximately 4 to 10 minutes. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol is 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.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
P O Box 2825
Shortland Street
Auckland 1140
New Zealand
Free Phone 0800 233 988

9. DATE OF FIRST APPROVAL

19 April 2007

10. DATE OF REVISION OF THE TEXT

14 May 2020

Summary table of changes

Section changed	Summary of new information

6.4	MEC - Update of shelf life

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