

NDA 21-779/S-008

Page 3

Ventavis® (iloprost) Inhalation Solution

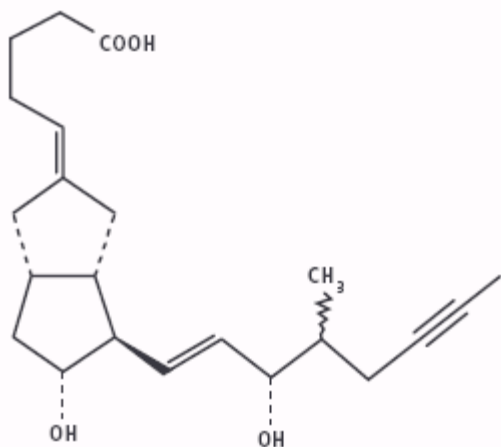
RX Only

RX Only

DESCRIPTION

Ventavis (iloprost) Inhalation Solution is a clear, colorless, sterile solution containing 10 mcg/mL iloprost formulated for inhalation via either of two pulmonary drug delivery devices: the I-neb® AAD® (Adaptive Aerosol Delivery) System or the Prodose® AAD® System. Ventavis is supplied in 2 ampule configurations, a 2 mL and a 1 mL single-use glass ampule. Both ampule sizes contain 10 mcg/1 mL. Each mL of the aqueous solution contains 0.01 mg iloprost, 0.81 mg ethanol, 0.121 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.51 mg hydrochloric acid (for pH adjustment to 8.1) in water for injection. The solution contains no preservatives.

The chemical name for iloprost is (E)-(3*aS*, 4*R*, 5*R*, 6*aS*)-hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]- $\Delta^{2(1H),\Delta}$ -pentalenevaleric acid. Iloprost consists of a mixture of the 4*R* and 4*S* diastereomers at a ratio of approximately 53:47. Iloprost is an oily substance, which is soluble in methanol, ethanol, ethyl acetate, acetone and pH 7 buffer, sparingly soluble in buffer pH 9, and very slightly soluble in distilled water, buffer pH 3, and buffer pH 5. The molecular formula of iloprost is C₂₂H₃₂O₄. Its relative molecular weight is 360.49. The structural formula is shown below:



CLINICAL PHARMACOLOGY

General

Iloprost is a synthetic analogue of prostacyclin PGI₂. Iloprost dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation but the relevance of this effect to the treatment of pulmonary hypertension is unknown. The two diastereo isomers of iloprost differ in their potency in dilating blood vessels, with the 4*S* isomer substantially more potent than the 4*R* isomer.

Pharmacokinetics

General

In pharmacokinetic studies in animals, there was no evidence of interconversion of the two diastereoisomers of iloprost. In human pharmacokinetic studies, the two diastereoisomers were not individually assayed.

NDA 21-779/S-008

Page 4

Iloprost administered intravenously has linear pharmacokinetics over the dose range of 1 to 3 ng/kg/min. The half-life of iloprost is 20 to 30 minutes. Following inhalation of iloprost (5 mcg) patients with pulmonary hypertension have iloprost peak serum levels of approximately 150 pg/mL. Iloprost was generally not detectable in the plasma 30 minutes to 1 hour after inhalation.

Absorption and Distribution

The absolute bioavailability of inhaled iloprost has not been determined.

Following intravenous infusion, the apparent steady-state volume of distribution was 0.7 to 0.8 L/kg in healthy subjects. Iloprost is approximately 60% protein-bound, mainly to albumin, and this ratio is concentration-independent in the range of 30 to 3000 pg/mL.

Metabolism and Excretion

Clearance in normal subjects was approximately 20 mL/min/kg. Iloprost is metabolized principally via β -oxidation of the carboxyl side chain. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. In animal experiments, tetranor-iloprost was pharmacologically inactive.

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

A mass-balance study using intravenously and orally administered [3 H]-iloprost in healthy subjects (n=8) showed recovery of total radioactivity over 14 hours post-dose, was 81%, with 68% and 12% recoveries in urine and feces, respectively.

Special Populations

Liver Function Impairment

Inhaled iloprost has not been evaluated in subjects with impaired hepatic function. However, in an intravenous iloprost study in patients with liver cirrhosis, the mean clearance in Child Pugh Class B subjects (n=5) was approximately 10 mL/min/kg (half that of healthy subjects). Following oral administration, the mean AUC_{0-8h} in Child Pugh Class B subjects (n=3) was 1725 pg*h/mL compared to 117 pg*h/mL in normal subjects (n=4) receiving the same oral iloprost dose. In Child Pugh Class A subjects (n=5), the mean AUC_{0-8h} was 639 pg*h/mL. Although exposure increased with hepatic impairment, there was no effect on half-life.

Renal Function Impairment

Inhaled iloprost has not been evaluated in subjects with impaired renal function. However, in a study with intravenous infusion of iloprost in patients with end-stage renal failure requiring intermittent dialysis treatment (n=7), the mean AUC_{0-4h} was 230 pg*h/mL compared to 54 pg*h/mL inpatients with renal failure (n=8) not requiring intermittent dialysis and 48 pg*h/mL in normals. The half-life was similar in both groups. The effect of dialysis on iloprost exposure has not been evaluated.

Clinical Trials

A randomized, double-blind, multi-center, placebo-controlled trial was conducted in 203 adult patients (inhaled iloprost: n=101; placebo: n=102) with NYHA Class III or IV pulmonary arterial hypertension (PAH, WHO

NDA 21-779/S-008

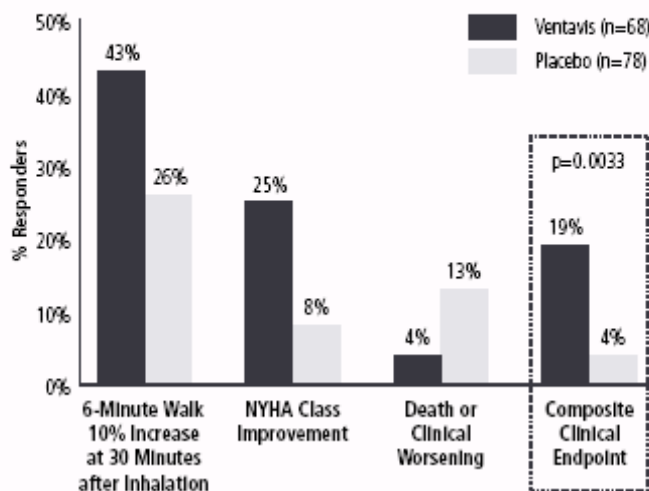
Page 5

Group I; idiopathic in 53%, associated with connective tissue disease, including CREST and scleroderma, in 17%, or associated with anorexigen use in 2%) or pulmonary hypertension related to chronic thromboembolic disease (WHO Group IV; 28%). Inhaled iloprost (or placebo) was added to patients' current therapy, which could have included anticoagulants, vasodilators (e.g. calcium channel blockers), diuretics, oxygen, and digitalis, but not PGI₂ (prostacyclin or its analogues) or endothelin receptor antagonists. Patients received 2.5 or 5.0 mcg of iloprost by repeated inhalations 6 to 9 times per day during waking hours. The mean age of the entire study population was 52 years and 68% of the patients were female. The majority of patients (59%) were NYHA Class III. The baseline 6-minute walk test values reflected a moderate exercise limitation (the mean was 332 meters for the iloprost group and 315 meters for the placebo group). In the iloprost group, the median daily inhaled dose was 30 mcg (range of 12.5 to 45 mcg/day). The mean number of inhalations per day was 7.3. Ninety percent of patients in the iloprost group never inhaled study medication during the nighttime.

The primary efficacy endpoint was clinical response at 12 weeks, a composite endpoint defined by: a) improvement in exercise capacity (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing, b) improvement by at least one NYHA class versus baseline, and c) no death or deterioration of pulmonary hypertension. Deterioration required two or more of the following criteria: 1) refractory systolic blood pressure < 85 mmHg, 2) worsening of right heart failure with cardiac edema, ascites, or pleural effusion despite adequate background therapy, 3) rapidly progressive cardiogenic hepatic failure (e.g. leading to an increase of GOT or GPT to > 100 U/L, or total bilirubin \geq 5 mg/dL), 4) rapidly progressive cardiogenic renal failure (e.g. decrease of estimated creatinine clearance to \leq 50% of baseline), 5) decrease in 6-minute walking distance by \geq 30% of baseline value, 6) new long-term need for i.v. catecholamines or diuretics, 7) cardiac index \leq 1.3 L/min/m², 8) CVP \geq 22 mmHg despite adequate diuretic therapy, and 9) SVO₂ \leq 45% despite nasal O₂ therapy.

Although effectiveness was seen in the full population (response rates for the primary composite endpoint of 17% and 5%; p=0.007), there was inadequate evidence of benefit in patients with pulmonary hypertension associated with chronic thromboembolic disease (WHO Group IV); the results presented are therefore those related to patients with PAH (WHO Group I). The response rate for the primary efficacy endpoint among PAH patients was 19% for the iloprost group, compared with 4% for the placebo group (p=0.0033). All three components of the composite endpoint favored iloprost (Figure 1).

Figure 1: Composite Primary Endpoint for PAH Patients (WHO Group I)

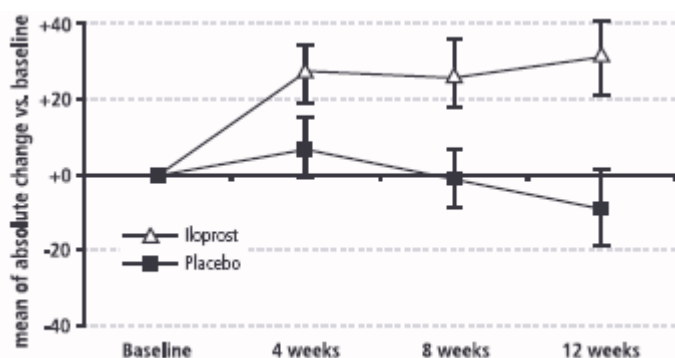


NDA 21-779/S-008

Page 6

The absolute change in 6-minute walk distance (Figure 2) measured (using all available data and no imputation) 30 minutes after inhalation among patients with PAH was greater in the iloprost group compared to the placebo group at all time points. At Week 12, the placebo-corrected difference was 40 meters ($p < 0.01$). When walk distance was measured immediately prior to inhalation, the improvement compared to placebo was approximately 60% of the effect seen at 30 minutes after inhalation.

Figure 2: Change (Mean \pm SEM) in 6-Minute Walk Distance 30 Minutes post Inhalation in PAH Patients (WHO Group I).



The effect of Ventavis in various subgroups is shown in Table 1.

Table 1: Treatment Effects by Subgroup among PAH Patients (WHO Group I)

	<u>Composite Clinical Endpoint</u>				<u>6-Minute Walk (m)*</u>			
	<u>n</u>	<u>Ventavis n (%)</u>	<u>n</u>	<u>Placebo n (%)</u>	<u>n</u>	<u>Ventavis (mean \pmSD)</u>	<u>n</u>	<u>Placebo (mean \pmSD)</u>
All Subjects with PAH	68	13 (19%)	78	3 (4%)	64	31 \pm 76	65	-9 \pm 79
NYHA III	40	7 (18%)	47	2 (4%)	39	24 \pm 72	43	-16 \pm 86
NYHA IV	28	6 (21%)	31	1 (3%)	25	43 \pm 82	22	6 \pm 63
Male	23	5 (22%)	24	0 (0%)	21	37 \pm 81	21	-22 \pm 77
Female	45	8 (18%)	54	3 (6%)	43	29 \pm 74	44	-2 \pm 81
Age \leq 55	41	6 (15%)	40	2 (5%)	39	24 \pm 79	32	-5 \pm 78
Age > 55	27	7 (26%)	38	1 (3%)	25	42 \pm 71	33	-13 \pm 81

* Change from baseline to 12 Weeks with measurement 30 minutes after dosing, based on all available data.

NDA 21-779/S-008

Page 7

Hemodynamic assessments obtained at week 12 before inhalation in both groups (at least 2 hours after a previous dose, trough) and after inhalation in the iloprost group (approximately 15 minutes after a dose, peak), are shown in Table 2. The relationship between hemodynamic changes and clinical effects is unknown.

Table 2: Hemodynamic Parameters Before and After Iloprost Inhalation: Change from Baseline to Week 12

Parameter	Baseline		Mean (\pm SD) change from baseline at Week 12		
	Iloprost	Placebo	Iloprost		Placebo
			Before Inhalation	After Inhalation	
PVR ($\text{dyn}\cdot\text{s}\cdot\text{cm}^{-5}$)	1029 \pm 390	1041 \pm 493	-9 \pm 275 (n=76)	-239 \pm 279 (n=70)	+96 \pm 323 (n=77)
mPAP (mmHg)	53 \pm 12	54 \pm 14	-0.2 \pm 7.3 (n=93)	-4.6 \pm 9.3 (n=90)	-0.1 \pm 6.9 (n=82)
CO (L/min)	3.8 \pm 1.1	3.8 \pm 0.9	+0.1 \pm 0.9 (n=91)	+0.5 \pm 1.1 (n=89)	-0.2 \pm 0.8 (n=80)
SVO ₂ (%)	60 \pm 8	60 \pm 8	-1.1 \pm 7.6 (n=72)	+1.8 \pm 8.3 (n=70)	-3.2 \pm 6.7 (n=63)

In a small, randomized, double-blind, placebo-controlled study (the STEP trial), 34 patients treated with bosentan 125 mg bid for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

INDICATIONS AND USAGE

Ventavis is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms. In controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration (see CLINICAL PHARMACOLOGY, Clinical Trials).

CONTRAINDICATIONS

There are no known contraindications.

WARNINGS

Ventavis is intended for inhalation administration only via either of two pulmonary drug delivery devices: the Ineb® AAD® System or the Prodose® AAD® System (See **DOSAGE AND ADMINISTRATION**). It has not been studied with any other nebulizers.

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 blood pressure less than 85 mmHg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

NDA 21-779/S-008

Page 8

Should signs of pulmonary edema occur when inhaled iloprost is administered in patients with pulmonary hypertension, the treatment should be stopped immediately. This may be a sign of pulmonary venous hypertension.

PRECAUTIONS

General

Ventavis solution should not be allowed to come into contact with the skin or eyes; oral ingestion of Ventavis solution should be avoided.

Direct mixing of Ventavis with other medications in the I-neb® AAD® System or the Prodose® AAD® System has not been evaluated.

Ventavis inhalation can induce bronchospasm, especially in susceptible patients with hyperreactive airways. Ventavis has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections. **Such patients should be carefully monitored during therapy with Ventavis.**

Information for Patients

Patients receiving Ventavis should be advised to use the drug only as prescribed with either of two pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose® AAD® System, following the manufacturer's instructions (see **DOSAGE AND ADMINISTRATION**). Patients should be trained in proper administration techniques including dosing frequency, ampule dispensing, I-neb® AAD® System or the Prodose® AAD® System operation, and equipment cleaning.

Patients should be advised that they may have a fall in blood pressure with Ventavis, so they may become dizzy or even faint. They should stand up slowly when they get out of a chair or bed. If fainting gets worse, patients should consult their physicians about dose adjustment.

Patients should be advised that Ventavis should be inhaled at intervals of not less than 2 hours and that the acute benefits of Ventavis may not last 2 hours.

Drug Interactions

In studies in normal volunteers, there was no pharmacodynamic interaction between intravenous iloprost and either nifedipine, diltiazem, or captopril. However, iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Since iloprost inhibits platelet function, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants. During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, corticosteroids, and other medications. Intravenous infusion of iloprost had no effect on the pharmacokinetics of digoxin. Acetylsalicylic acid did not alter the clearance (pharmacokinetics) of iloprost. Although clinical studies have not been conducted, *in vitro* studies of iloprost indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Iloprost was not mutagenic in bacterial and mammalian cells in the presence or absence of extrinsic metabolic activation. Iloprost did not cause chromosomal aberrations *in vitro* in human lymphocytes and was not clastogenic *in vivo* in NMRI/SPF mice. There was no evidence of a tumorigenic effect of iloprost clathrate (13% iloprost by weight) in Sprague-Dawley rats dosed orally for up to 8 months at doses of up to 125 mg/kg/day (C_{max} of 45 ng/mL serum), followed by 16 months at 100 mg/kg/day, or in CrI:CD-1®(ICR)BR albino mice dosed orally for up to 24 months at doses of up to 125 mg/kg/day (C_{max} of 156 ng/mL serum). The

NDA 21-779/S-008

Page 9

recommended clinical dosage regimen for iloprost (5 mcg) affords a serum C_{max} of 0.16 ng/mL. Fertility of males or females was not impaired in Han-Wistar rats at intravenous doses up to 1 mg/kg/day.

Pregnancy

Pregnancy Category C. In developmental toxicity studies in pregnant Han-Wistar rats, continuous intravenous administration of iloprost at a dosage of 0.01 mg/kg daily (serum levels not available) led to shortened digits of the thoracic extremity in fetuses and pups. In comparable studies in pregnant Sprague-Dawley rats which received iloprost clathrate (13% iloprost by weight) orally at dosages of up to 50 mg/kg/day (C_{max} of 90 ng/mL), in pregnant rabbits at intravenous dosages of up to 0.5 mg/kg/day (C_{max} of 86 ng/mL), and in pregnant monkeys at dosages of up to 0.04 mg/kg/day (serum levels of 1 ng/mL), no such digital anomalies or other gross-structural abnormalities were observed in the fetuses/pups. However, in gravid Sprague-Dawley rats, iloprost clathrate (13% iloprost) significantly increased the number of non-viable fetuses at a maternally toxic oral dosage of 250 mg/kg/day and in Han-Wistar rats was found to be embryolethal in 15 of 44 litters at an intravenous dosage of 1 mg/kg/day. There are no adequate and well-controlled studies in pregnant women. Ventavis should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether Ventavis is excreted in human milk. In studies with Han-Wistar rats, higher mortality was observed in pups of lactating dams receiving iloprost intravenously at 1 mg/kg daily. In Sprague-Dawley rats, higher mortality was also observed in nursing pups at a maternally toxic oral dose of 250 mg/kg/day of iloprost clathrate (13% iloprost by weight). It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Ventavis, a decision to discontinue nursing should be made, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Ventavis did not include sufficient numbers of subjects age 65 and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Hepatic or Renal Impairment

Ventavis has not been studied in patients with pulmonary hypertension and hepatic or renal impairment, both of which increase mean AUC in otherwise normal subjects (see **CLINICAL PHARMACOLOGY, Special Populations**).

ADVERSE REACTIONS

Pre-marketing experiences

Pre-marketing safety data on Ventavis were obtained from 215 patients with pulmonary arterial hypertension receiving iloprost in two 12-week clinical trials and two long-term extensions. Patients received inhaled

NDA 21-779/S-008

Page 10

Ventavis for periods of from 1 day to more than 3 years. The median number of weeks of exposure was 15 weeks. Forty patients completed 12 months of open-label treatment with iloprost.

The following table shows adverse events reported by at least 4 iloprost patients and reported at least 3% more frequently for iloprost patients than placebo patients in the 12-week placebo-controlled study.

Table 3: Adverse Events in Phase 3 Clinical Trial

Adverse Event	Iloprost n = 101	Placebo n = 102	Placebo subtracted %
Vasodilation (flushing)	27	9	18
Cough increased	39	26	13
Headache	30	20	10
Trismus	12	3	9
Insomnia	8	2	6
Nausea	13	8	5
Hypotension	11	6	5
Vomiting	7	2	5
Alk phos increased	6	1	5
Flu syndrome	14	10	4
Back pain	7	3	4
Abnormal lab test	7	3	4
Tongue pain	4	0	4
Palpitations	7	4	3
Syncope	8	5	3
GGT increased	6	3	3
Muscle cramps	6	3	3
Hemoptysis	5	2	3
Pneumonia	4	1	3

Pre-marketing serious adverse events reported with the use of inhaled iloprost and not shown in Table 3 include congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure.

In a small clinical trial (the STEP trial, see **CLINICAL TRIALS**), safety trends in patients receiving concomitant bosentan and iloprost were consistent with those observed in the larger experience of the Phase 3 study in patients receiving only iloprost.

Adverse events with higher doses

In a study in healthy volunteers (n=160), inhaled doses of iloprost solution were given every 2 hours, beginning with 5 mcg and increasing up to 20 mcg for a total of 6 dose inhalations (total cumulative dose of 70 mcg) or up to the highest dose tolerated in a subgroup of 40 volunteers. There were 13 subjects (32%) who failed to reach the highest scheduled dose (20 mcg). Five were unable to increase the dose because of (mild to moderate) transient chest pain/discomfort/tightness, usually accompanied by headache, nausea, and dizziness. The remaining 8 subjects discontinued for other reasons.

POSTMARKETING EXPERIENCE

NDA 21-779/S-008

Page 11

The following adverse reactions have been identified during the postapproval use of Ventavis. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of bronchospasm and wheezing have been reported, particularly in susceptible patients with hyperreactive airways, such as patients with comorbid diseases affecting the airways (see PRECAUTIONS). Cases of epistaxis and gingival bleeding have been reported within one month of starting iloprost treatment. Cases of dizziness and diarrhea have also been reported with the use of Ventavis.

OVERDOSAGE

In clinical trials of Ventavis, no case of overdose was reported. Signs and symptoms to be anticipated are extensions of the dose-limiting pharmacological effects, including hypotension, headache, flushing, nausea, vomiting, and diarrhea. A specific antidote is not known. Interruption of the inhalation session, monitoring, and symptomatic measures are recommended.

DOSAGE AND ADMINISTRATION

Ventavis is intended to be inhaled using either of two pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose® AAD® System. The first inhaled dose should be 2.5 mcg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 mcg and maintained at that dose; otherwise maintain the dose at 2.5 mcg. Ventavis should be taken 6 to 9 times per day (no more than once every 2 hours) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mcg (5 mcg 9 times per day).

Direct mixing of Ventavis with other medications in the I-neb® AAD® System or the Prodose® AAD® System has not been evaluated. To avoid potential interruptions in drug delivery due to equipment malfunctions, the patient should have easy access to a back-up I-neb® AAD® System or the Prodose® AAD® System.

Ventavis is supplied in two ampule configurations, a 2mL and a 1mL single-use glass ampule. Both ampule sizes contain 10 mcg/1mL.

The 2mL single-use ampule delivers 20 mcg to the medication chamber of either of the AAD® Delivery Systems. The 2mL must be used with the Prodose® AAD® System and may be used with the I-neb® AAD® System.

The 1 mL ampule delivers 10 mcg to the medication chamber and must only be used with the I-neb® AAD® System.

Both the 2mL and the 1 mL ampules deliver a nominal dose of either 2.5 mcg or 5.0 mcg at the mouthpiece of the AAD® Delivery System for which they are labeled for use.

Each inhalation treatment requires one single-use ampule.

For each inhalation session, the entire contents of one opened ampule of Ventavis should be transferred into either the I-neb® AAD® System or the Prodose® AAD® System medication chamber (2 mL ampule only) immediately before use. After each inhalation session, any solution remaining in the medication chamber should be discarded. Use of the remaining solution will result in unpredictable dosing. Patients should follow the manufacturer's instructions for cleaning the I-neb® AAD® System or the Prodose® AAD® System components after each dose administration.

NDA 21-779/S-008

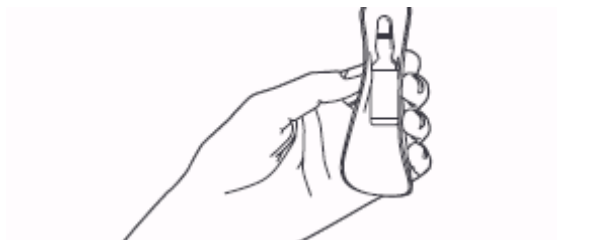
Page 12

Preparation

1. With one hand, hold the bottom of the ampule with the blue dot facing away from your body.



2. With the other hand, wrap the included rubber pad round the entire ampule.



3. Using your thumbs, break open the neck of the ampule by snapping the top towards you.



4. Using the small tube (pipette) supplied with Ventavis, draw-up the entire amount of one ampule of Ventavis and transfer the entire contents of the ampule into the medication chamber of either the I-neb® AAD® System or the Prodose® AAD® System.



5. Safely dispose of the open ampule and pipette as instructed by your healthcare practitioner. Keep ampules and pipettes out of the reach of children.

NDA 21-779/S-008

Page 13



6. Follow the instructions provided by the drug manufacturer for administration of the Ventavis dose and maintenance of the I-neb® AAD® System or the Prodose® AAD® System.

Should patients deteriorate on this treatment, alternative treatments should be considered. Several patients whose status deteriorated while on Ventavis were successfully switched to intravenous epoprostenol.

Dosage and Administration in Hepatic Impairment

Because iloprost elimination is reduced in patients with impaired liver function (see **CLINICAL PHARMACOLOGY and PRECAUTIONS**), caution should be exercised during iloprost therapy in patients with at least Child Pugh Class B hepatic impairment.

Dosage and Administration in Renal Impairment

Dose adjustment is not required in patients not on dialysis. The effect of dialysis on iloprost is unknown. Use caution in treating patients on dialysis (see **CLINICAL PHARMACOLOGY and PRECAUTIONS**).

HOW SUPPLIED

Ventavis (iloprost) Inhalation Solution is supplied in two ampule configurations, 2 mL and 1mL:

For the 2mL ampule Ventavis is supplied in cartons of 30 clear glass single-use ampules (20 mcg iloprost per 2mL ampule):

30 single-use ampule cartons: NDC 10148-101-30

For the 1 mL ampule Ventavis is supplied in cartons of 30 clear glass single-use ampules (10 mcg iloprost per 1mL ampule):

30 single-use ampule cartons: NDC 66215-302-30

STORAGE

Store at 20 – 25°C (68 – 77°F)

Excursions permitted to 15 – 30°C (59 – 86°F)

[See USP Controlled Room Temperature]

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NDA 21-779/S-008

Page 14

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PATIENT INFORMATION

Ventavis[®] (ven TAY vis) Inhalation Solution (iloprost)

Read the Patient Information that comes with Ventavis before you start using it and each time you get a refill. There may be new information. The leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT VENTAVIS?

Ventavis may cause dizziness, lightheadedness, and fainting (syncope) because it lowers your blood pressure. These are also common symptoms of pulmonary arterial hypertension (PAH).

- To reduce your chances of fainting, stand up slowly when you get out of chairs or bed.
- Use Ventavis before increased physical exertion.
- Tell your doctor if fainting gets worse with Ventavis. Your doctor may need to adjust your dose or change your treatment.

Do not drive a car or operate any tools or machines if dizziness or fainting from low blood pressure is a problem for you.

WHAT IS VENTAVIS?

Ventavis is a prescription medicine for adults with certain kinds of severe PAH. It is used to improve exercise ability and symptoms for a short time. PAH is a condition where blood pressure is too high in the blood vessels between the heart and the lungs.

Ventavis has not been studied in children under the age of 18.

HOW DOES VENTAVIS WORK?

Ventavis lowers blood pressure within the pulmonary arteries by opening up the blood vessels in the lungs.

WHAT SHOULD I TELL MY DOCTOR BEFORE STARTING VENTAVIS?

Tell your doctor about all of your medical conditions including if you:

- **have liver or kidney problems.** Your doctor may need to give you a lower dose of Ventavis.
- **are pregnant, or planning to become pregnant.** It is not known if Ventavis can harm your unborn baby.

NDA 21-779/S-008

Page 15

Ventavis should be used during pregnancy only if clearly needed. Women who can get pregnant should use effective birth control during treatment with Ventavis. Talk to your doctor about effective birth control methods.

- **are breast-feeding. It is not known if Ventavis passes into your milk.** Talk to your doctor about the best way to feed your baby while using Ventavis.

Tell your doctor about all the medicines you are taking including prescription and nonprescription medicines, vitamins, and herbal supplements. Ventavis and certain other medicines may affect each other in the way they work in your body. Be sure to tell your doctor if you take:

- medicines used to treat high blood pressure or heart disease
- medicines that decrease blood clotting

Keep a list of all the medicines you take. Show this list to your doctor and pharmacist each time you get a new medicine.

HOW SHOULD I TAKE VENTAVIS?

See the end of this leaflet for instructions for using Ventavis with the Prodose[®] AAD[®] System or I-neb[®] AAD[®] System.

- **Take Ventavis exactly as prescribed by your doctor.** Ventavis is usually used 6 to 9 times a day during waking hours. Your doctor will tell you how to space your doses. You should take Ventavis when you wake up and also before any physical activity, but not more frequently than every 2 hours. Do not change your dose without talking to your doctor.
- Ventavis is breathed (inhaled) into your lungs with the help of the Prodose[®] AAD[®] System or I-neb[®] AAD[®] System. One treatment session will usually last about 4 to 10 minutes.
- **Do not drink Ventavis.**
- **Do not let Ventavis solution come into contact with your skin or eyes.** If it does, rinse the skin or your eyes right away with water.
- If you take too much Ventavis, you may get a severe headache, chest pain, reddening of the face, jaw pain, dizziness, nausea, vomiting and diarrhea. If this happens stop taking Ventavis. If symptoms persist, call your doctor.
- Do not allow other people to be exposed to Ventavis while you are breathing it, especially babies and pregnant women.

WHAT ARE THE SIDE EFFECTS WITH VENTAVIS?

Ventavis may cause dizziness, lightheadness, and fainting (syncope) because it lowers your blood pressure. See “What is the most important information I should know about Ventavis?”

The most common side effects with Ventavis include reddening of the face caused by dilation of blood vessels (flushing), increased cough, low blood pressure (hypotension), headaches, nausea, spasm of the jaw muscles that causes trouble opening your mouth, and fainting (syncope).

Talk to your doctor about any side effect that bothers you or that does not go away.

These are not all of the side effects with Ventavis. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at **1-800-FDA 1088**.

NDA 21-779/S-008

Page 16

HOW SHOULD I STORE VENTAVIS?

- Store Ventavis ampules at **68 to 77°F (20 to 25°C)**.
- Safely dispose of Ventavis that is out of date or no longer needed.
- **Keep Ventavis and all medicines out of the reach of children.**

GENERAL INFORMATION ABOUT VENTAVIS

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use Ventavis for a condition for which it was not prescribed. Do not give Ventavis to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about Ventavis. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about Ventavis that was written for healthcare professionals. Additional information can be found at **www.4VENTAVIS.com** or by calling 1-877-4VENTAVIS (1-877-483-6828).

WHAT ARE THE INGREDIENTS IN VENTAVIS?

Active ingredient: iloprost. Each ampule contains 10 micrograms per mL of iloprost. 2 mL ampules contain 20 micrograms of iloprost and 1 mL ampules contain 10 micrograms of iloprost.

Inactive ingredients: tromethamine, ethanol, sodium chloride, hydrochloric acid for pH adjustment, and water for injection.

INSTRUCTIONS FOR USING VENTAVIS WITH THE PRODOSE[®] AAD[®] SYSTEM OR THE I-NEB[®] AAD[®] SYSTEM

Do not use Ventavis until your doctor or other healthcare provider has trained you on how to use the Prodose[®] AAD[®] System or the I-neb[®] AAD[®] System. Make sure you understand all the instructions or ask questions until you do.

Ventavis should only be taken using the Prodose[®] AAD[®] System or the I-neb[®] AAD[®] System. The Prodose[®] AAD[®] System or the I-neb[®] AAD[®] System has been made to deliver the right dose of Ventavis. Using other devices is not recommended and other devices may not deliver the prescribed amount of Ventavis.

If you are using the Prodose[®] AAD[®] System, your doctor will give you 2 dosing discs for your Prodose[®] AAD[®] System. These dosing discs will control the amount of Ventavis you use. **Do not change the dosing disc in your Prodose[®] AAD[®] System without talking to your doctor. Always use the entire contents of a 2 mL ampule when using your Prodose[®] AAD[®] System.** Using less than the 2 mL of liquid may not provide you with enough medication.

If you are using the I-neb[®] AAD[®] System, your doctor will give you two medication chambers (one with a red latch and one with a purple latch) and two color matching control discs. The medication chamber controls the amount of Ventavis you use. The medication chamber with the red latch delivers the 2.5 microgram dose and the medication chamber with the purple latch delivers the 5.0 microgram dose. The matching control disc operates the I-neb[®] AAD[®] System. The red control disc should be used with the red-latched medication chamber, and the purple control disc should be used with the purple-latched medication chamber. **Do not change the**

NDA 21-779/S-008

Page 17

medication chamber and control disc in your I-neb® AAD® System without talking to your doctor.

Do not put any medicines other than Ventavis in your Prodose® AAD® System or I-neb® AAD® System.

TO USE VENTAVIS:

1. Open the small glass bottle (ampule) of Ventavis by:
 - holding the ampule with the blue dot facing away from your body



- wrapping the included rubber pad around the ampule to protect from getting cut



- using your thumbs to break open the neck of the ampule by snapping the top towards you



2. Using the small tube (pipette) that comes with Ventavis, draw-up the entire amount of one ampule of Ventavis and empty it into the center of the Prodose® AAD® System or the I-neb® AAD® System medicine chamber. The amount of Ventavis you receive will be controlled by either the dosing disc or the medication chamber that has been prescribed for you.



3. Safely dispose of the open ampule and pipette as instructed by your healthcare practitioner. Keep both out of the reach of children.



4. Follow the instructions that come with your Prodose® AAD® System or I-neb® AAD® System for using it to breathe in your dose of Ventavis. Each treatment session with Ventavis lasts about 4 to 10 minutes. The Prodose® AAD® System or I-neb® AAD® System allows you to interrupt your treatment for up to ten minutes with no effect on the final dose you receive. If your treatment is interrupted for more than ten minutes, the Prodose® AAD® System or I-neb® AAD® System will reset itself. In such cases, **you should discard the remaining solution in the chamber and wait at least two hours before taking your next dose. Taking a second dose immediately could result in receiving too much medication.**
5. After each treatment dispose of any Ventavis that is left in the Prodose® AAD® System or the I-neb® AAD® System medicine chamber. Use of the remainder of Ventavis will not give you the right dose.
6. Follow the instructions that come with the Prodose® AAD® System or the I-neb® AAD® System for cleaning it after each treatment.
7. Make sure you have a back-up Prodose® AAD® System or I-neb® AAD® System to use for Ventavis

