

**FOR PULMONARY
ARTERIAL HYPERTENSION
(PAH) NYHA CLASS III OR IV**

SECOND WIND® IN PAH

**The only inhaled PAH
therapy to demonstrate a
spectrum of PAH efficacy**

- **Significant clinical improvement ($p=0.0033$)^{1,2}**
- **Significant functional class improvement ($p=0.03$)^{1,2}**
- **Significant hemodynamic improvement (PVR, CO, and mPAP; $p<0.001$)^{1,2}**
- **Significant 6MWD improvement ($p<0.01$)^{1,2}**

AIR PIVOTAL TRIAL

Randomized, double-blind, multicenter, placebo-controlled trial to evaluate the efficacy and safety of Ventavis monotherapy compared with placebo in the treatment of PAH (WHO Group I) NYHA Class III or IV (n=146). Clinical improvement is a combined endpoint defined as $\geq 10\%$ increase in 6-minute walk distance (6MWD), improvement by at least 1 NYHA functional class, and lack of clinical worsening events or death.

IMPORTANT SAFETY INFORMATION: In clinical studies, common adverse reactions due to Ventavis included vasodilation (flushing), cough, headache, trismus, and insomnia. Serious adverse events reported at a rate of less than 3% included congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure. Vital signs should be monitored while initiating Ventavis. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mm Hg. Stop Ventavis immediately if signs of pulmonary edema occur; this may be a sign of pulmonary venous hypertension.

Please see brief summary of prescribing information on following page.

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"Second Wind" is a licensed trademark of Pulmonary Rehabilitation Associates.



Smart technology from the I-neb AAD by Philips Respironics



**A spectrum of
inhaled PAH efficacy**

www.4ventavis.com



BRIEF SUMMARY

The following is a brief summary of the Full Prescribing Information for Ventavis (iloprost) Inhalation Solution. Please review the Full Prescribing Information prior to prescribing Ventavis.

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 section of Full Prescribing Information**).

CONTRAINDICATIONS

There are no known contraindications.

WARNINGS

Ventavis is intended for inhalation administration only via either of two pulmonary drug delivery devices: the I-neb[®] AAD[®] System or the Prodose[®] AAD[®] System (see **DOSE AND ADMINISTRATION section of Full Prescribing Information**). 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 mm Hg. 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.

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 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 **DOSE AND ADMINISTRATION section of Full Prescribing Information**). 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 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 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 section of Full Prescribing Information**).

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 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.

Table 1 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.

Pre-marketing serious adverse events reported with the use of inhaled iloprost and not shown in Table 1 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 section of Full Prescribing Information**), 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.

Table 1: 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

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

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 section of Full Prescribing Information**). 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.

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REFERENCES 1. Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med*. 2002;347:322-329. 2. Ventavis (iloprost) full prescribing information. Actelion Pharmaceuticals US, Inc. 2008.