HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VENTAVIS safely and effectively. See full prescribing information for VENTAVIS.

VENTAVIS® (iloprost) inhalation solution
Initial U.S. Approval: 2004
For oral inhalation only

INDICATIONS AND USAGE

Ventavis® is a synthetic analog of prostacyclin indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%). (1.1).

DOSAGE AND ADMINISTRATION

Ventavis is intended to be inhaled using the I-neb® AAD® System. Patients should receive 6 to 9 doses (inhalations) per day (minimum of 2 hours between doses during waking hours) as follows:

- Starting dose: 2.5 mcg (2.1).
- Uptitrate to 5 mcg if 2.5 mcg is well tolerated (2.1).
- Maintenance dose: 5 mcg (2.1).

	Delivered dose from ampule of :	
Nebulizer	10 mcg/mL	20 mcg/mL
I-neb® AAD®	2.5 or 5 mcg from one ampule	5 mcg from one ampule

- The 20 mcg/mL concentration is for patients who repeatedly experience extended treatment times (2.1).
- Vital signs should be monitored while initiating Ventavis (2.2).

DOSAGE FORMS AND STRENGTHS

1 mL ampules in two concentrations: 10 mcg/mL and 20 mcg/mL (3).

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Hypotension leading to syncope has been observed. Ventavis should not be administered in patients with systolic blood pressure below 85 mmHg (5.1).
- Pulmonary venous hypertension: Discontinue if pulmonary edema is present (5.2).
- May cause bronchospasm: Patients with a history of hyperreactive airway disease may be more sensitive (5.3).

ADVERSE REACTIONS

Most common (≥3% placebo adjusted) adverse reactions are vasodilation (flushing), cough increased, headache, trismus, insomnia, nausea, hypotension, vomiting, alkaline phosphatase increased, flu syndrome, back pain, tongue pain, palpitations, syncope, GGT increased, muscle cramps, hemoptysis, and pneumonia (6.1).
To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Ventavis has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents (7.2).
- There is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants (7.3).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: In patients with Child-Pugh Class B or C hepatic impairment, consider increasing the dosing interval (e.g., 3-4 hours between doses depending on the patient's response at the end of the dose interval) (2.3, 8.6).

See 17 for PATIENT COUNSELING INFORMATION and preparation instructions

Revised: 11/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

TABLE OF CONTENTS

***Sections or subsections omitted from the full prescribing information are not listed.**

1. INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

Ventavis® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%) *[see Clinical Studies (14)]*.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Ventavis is intended to be inhaled using the I-neb® 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 has not been evaluated; do not mix with other medications. 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.

Ventavis is supplied in 1 mL ampules in two concentrations: 10 mcg/mL and 20 mcg/mL.

	Delivered dose from ampule of :	
Nebulizer	10 mcg/mL	20 mcg/mL
I-neb® AAD®	2.5 or 5 mcg from one ampule	5 mcg from one ampule

The 20 mcg/mL concentration is intended for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Transitioning patients to the 20 mcg/mL concentration using the I-neb® AAD® System will decrease treatment times to help maintain patient compliance.

For each inhalation session, the entire contents of each opened ampule of Ventavis should be transferred into the I-neb® AAD® System medication chamber immediately before use *[see Patient Counseling Information (17.1)]*. 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 components after each dose administration.

2.2 Monitoring

Vital signs should be monitored while initiating Ventavis. *[see Warnings and Precautions (5.1)]*.

2.3 Use in Patients with Pre-existing Hepatic Impairment

Because iloprost elimination is reduced in patients with impaired liver function *[see Special Populations (8.6)]*, consider increasing the dosing interval (e.g., 3-4 hours between doses depending on the patient's response at the end of the dose interval) in patients with Child-Pugh Class B or C hepatic impairment.

2.4 Use in Patients with Pre-existing Renal Impairment

Dose adjustment is not required in patients who are not on dialysis. The effect of dialysis on iloprost is unknown *[see Special Populations (8.7)]*.

3. DOSAGE FORMS AND STRENGTHS

1 mL ampules in two concentrations: 10 mcg/mL and 20 mcg/mL.

4. CONTRAINDICATIONS

None

5. WARNINGS AND PRECAUTIONS

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

5.1 Risk of Syncope

Monitor vital signs while initiating Ventavis. Do not initiate Ventavis in patients with systolic blood pressure below 85 mmHg. 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.

5.2 Pulmonary Venous Hypertension

Should signs of pulmonary edema occur when inhaled Ventavis is administered in patients with pulmonary hypertension, stop treatment immediately, as this may be a sign of pulmonary venous hypertension.

5.3 Bronchospasm

Ventavis inhalation can induce bronchospasm. Bronchospasm may be more severe or frequent in patients with a history of hyperreactive airways. Ventavis has not been evaluated in patients with chronic obstructive pulmonary disease (COPD), severe asthma, or with acute pulmonary infections.

6. ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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. Forty patients completed 12 months of open-label treatment with iloprost.

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

Table 1: Adverse Events in Phase 3 Clinical Trial

Adverse Event	**Ventavis 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
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 Ventavis 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 Studies (14)]*, safety trends in patients receiving concomitant bosentan and Ventavis were consistent with those

observed in the larger experience of the Phase 3 study in patients receiving only Ventavis or bosentan.

Adverse events with higher doses

In a study in healthy subjects (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 subjects. 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.

6.2 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 patients with a history of hyperreactive airways *[see Warnings and Precautions (5.3)]*. Bleeding events most commonly reported as epistaxis and hemoptysis were observed on Ventavis treatment *[see Drug Interactions (7.3)]*. Cases of thrombocytopenia, dizziness, diarrhea, mouth and tongue irritation, nasal congestion, dysgeusia, hypersensitivity, and rash have also been reported with the use of Ventavis.

7. DRUG INTERACTIONS

During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatory drugs, 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.

7.1 Cytochrome P450

Although clinical studies have not been conducted with Ventavis (inhaled iloprost), *in vitro* studies of iloprost indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

7.2 Antihypertensives and Vasodilators

In studies in normal subjects, there was no pharmacodynamic interaction between intravenous iloprost and either nifedipine, diltiazem, or captopril. However, Ventavis has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents.

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