CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-779/S-009

Trade Name: Ventavis

Generic Name: iloprost

Sponsor: Actelion Clinical Research, Inc.

Approval Date: August 7, 2009

Purpose: Addition of a new strength of Ventavis 20 mcg/ml, and several revisions to the package insert and patient information leaflet

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-779/S-009

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-779/S-009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-779/S-009

Actelion Clinical Research, Inc.
Attention: Dr. Frances Duffy-Warren
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

SUPPLEMENT APPROVAL

Dear Dr. Duffy-Warren:

Please refer to your supplemental new drug application (sNDA) dated February 27, 2009, received March 2, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ventavis (iloprost) 10 mcg/mL Inhalation Solution.

This supplemental new drug application provides for the addition of a new strength of Ventavis 20 mcg/mL, and several revisions to the package insert and patient information leaflet.

Changes in the package insert are as follows:

DESCRIPTION: This section is being revised to add the description for the 1 mL ampules containing Ventavis (iloprost) 20 mcg/mL.

FROM

> 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/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.

TO

> Ventavis (iloprost) Inhalation Solution is a clear, colorless, sterile solution containing 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 1 mL single-use glass ampules containing either 10 mcg/mL or 20 mcg/mL.

For the 10 mcg/mL solution, one mL of the 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.

For the 20 mcg/mL solution, each mL of the solution contains 0.02 mg iloprost, 1.62 mg ethanol, 0.242 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.76 mg hydrochloric acid (for pH adjustment to 8.4) in water for injection.

PRECAUTIONS/Information for Patients: This section is being revised to add the following sentence to the last paragraph: "Thus patients may want to adjust times of administration to cover planned activities."

FROM

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.

TO

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. Thus patients may want to adjust times of administration to cover planned activities.

DOSAGE AND ADMINISTRATION: This section is being revised to:

- Add a separate set of instructions for opening sealed glass ampules using an ampule breaker (current instructions are for opening with the supplied rubber pad). These instructions are consistent with the instructions provided by the manufacturer of the ampule breaker.
- Provide instructions for the safe disposal of the top of the ampule into a sharps container.
- Add the instruction to use 2 x 1 mL ampules (instead of 1 x 2 mL ampule) for the Prodose AAD System now that the 2 mL ampules are no longer available.

FROM

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

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.

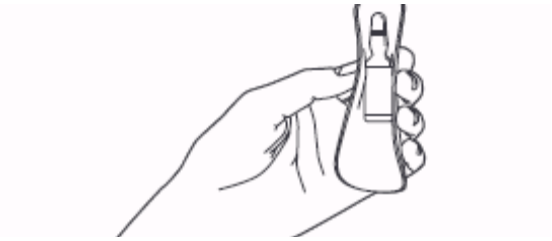
Each inhalation treatment requires one single-use ampule.

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.

Preparation

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

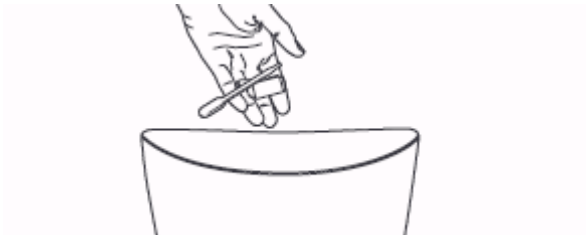
2. With the other hand, wrap the included rubber pad round the entire ampule.



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.



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.

TO

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
Prodose® AAD®	2.5 or 5 mcg from two ampules	N/A

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 either the I-neb® AAD® System or the Prodose® AAD® System medication chamber 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.

Preparation

Ventavis ampules may be opened with an ampule breaker or with a rubber pad.

When using a rubber pad:

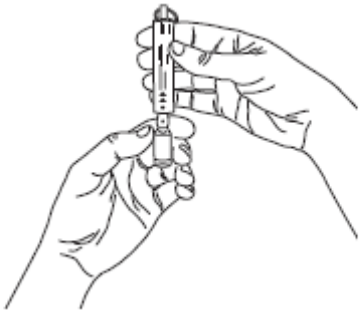
1. With one hand, hold the bottom of the ampule with the blue dot facing away from your body.

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

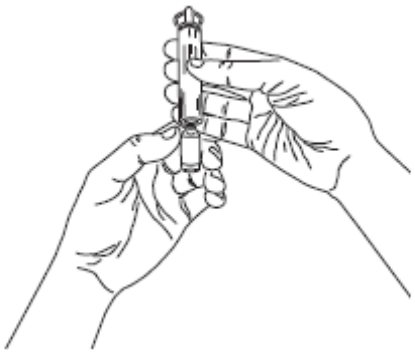
3. Using your thumbs, break open the neck of the ampule by snapping the top towards you and then carefully dispose of the top of the ampule into a sharps bin.

When using an ampule breaker:

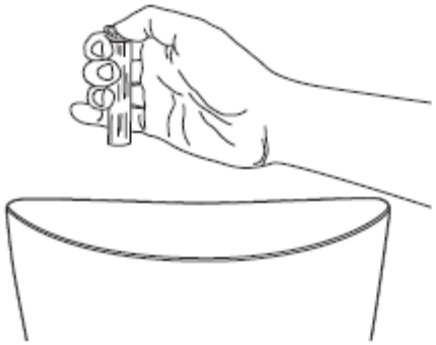
1. Align the blue dot on the Ventavis ampule with the dot on the ampule breaker, if available, and then insert the top of the ampule into the ampule breaker.



2. Gently break open the neck of the ampule by levering away from the dot on the Ventavis ampule to snap off the ampule lid.



3. Carefully dispose of the top of the ampule into a sharps bin or appropriate storage container.



4. After opening the ampules, use 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. If using the Prodose® AAD® System, two 10mcg/mL ampules need to be added to the medication chamber.

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.

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.

HOW SUPPLIED: This section is being revised to add the description for 1 mL ampules containing Ventavis (iloprost) 20 mcg/mL, cartons of 30, with the corresponding NDC number.

FROM

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

TO

Ventavis (iloprost) Inhalation Solutionis supplied in cartons of 30 x 1 mL clear glass single-use ampules as follows:

1 mL ampule containing iloprost 10 mcg per mL, carton of 30 (NDC 66215-302-30)

1 mL ampule containing iloprost 20 mcg per mL, carton of 30 (NDC 66215-303-30)

Also, changes to the patient information leaflet have been revised in several sections to reflect the addition of a new strength of Ventavis (iloprost), to ensure consistency in content between the patient and prescriber labeling text, and to improve overall readability.

We have completed our review of this application and it is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed agreed-upon labeling text.

Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 21-779/S-009**".

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS OF 21 CFR 314.81(b)(2)(vii)

We remind you of your postmarketing commitments in your submission dated August 5, 2009. These commitments are listed below:

1507-1

A study to verify that the 20 mcg/mL concentration of iloprost when used with the I-Neb AAD device does not change the extractable/leachable profile in comparison to the 10 mcg/mL concentration.

Final Report Submission: December 11, 2009

1507-2

A study to evaluate adsorption of the 20 mcg/mL concentration of iloprost to the I-Neb AAD device components.

Final Report Submission: December 11, 2009

Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Dan Brum, PharmD, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Agreed-upon Labeling Text

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
08/07/2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-779/S-009

LABELING

Ventavis® (iloprost) Inhalation Solution RX Only

RX Only

DESCRIPTION

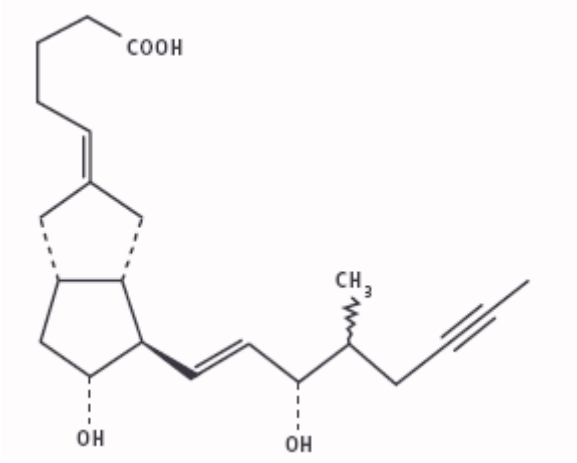
Ventavis (iloprost) Inhalation Solution is a clear, colorless, sterile solution containing iloprost formulated for inhalation via either of two pulmonary drug delivery devices: the I-neb® AAD® (Adaptive Aerosol Delivery) System or the Prodose® AAD® System. Ventavis is supplied in 1 mL single-use glass ampules containing either 10 mcg/mL or 20 mcg/mL.

For the 10 mcg/mL solution, one mL of the 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.

For the 20 mcg/mL solution, each mL of the solution contains 0.02 mg iloprost, 1.62 mg ethanol, 0.242 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.76 mg hydrochloric acid (for pH adjustment to 8.4) in water for injection.

The solution contains no preservatives.

The chemical name for iloprost is (E)-(3a*S*, 4*R*, 5*R*, 6a*S*)-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 4R and 4S 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 $C_{22}H_{32}O_4$. Its relative molecular weight is 360.49. The structural formula is shown below:



CLINICAL PHARMACOLOGY

General

Iloprost is a synthetic analogue of prostacyclin PGI_2. 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 4S isomer substantially more potent than the 4R 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.

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

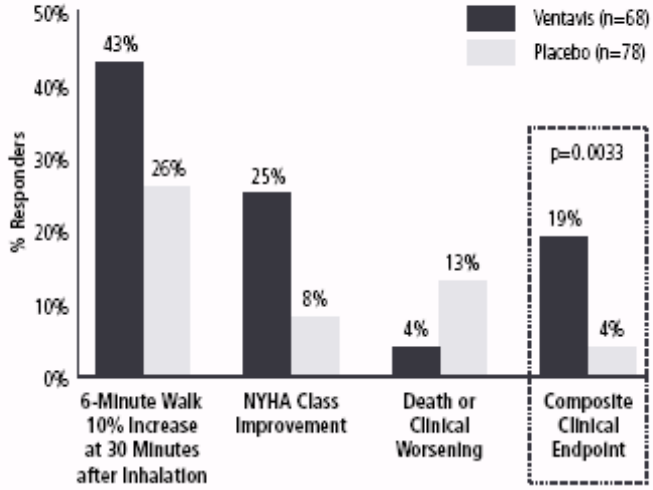
A randomized, double-blind, multi-center, placebo-controlled trial was conducted in 203 adult patients (inhaled iloprost: n=101; placebo: n=102) with NYHA Class III or IV pulmonary arterial hypertension (PAH, WHO Group I; idiopathic in 53%, associated with connective tissue disease, including CREST and 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 PGI_2 (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 ≥5 mg/dL), 4) rapidly progressive cardiogenic renal failure (e.g. decrease of estimated creatinine clearance to ≤ 50% of baseline), 5) decrease in 6-minute walking distance by ≥ 30% of baseline value, 6) new long-term need for i.v. catecholamines or diuretics, 7) cardiac index ≤ 1.3 L/min/m^2, 8) CVP ≥ 22 mmHg despite adequate diuretic therapy, and 9) SVO_2 ≤45% despite nasal O_2 therapy.

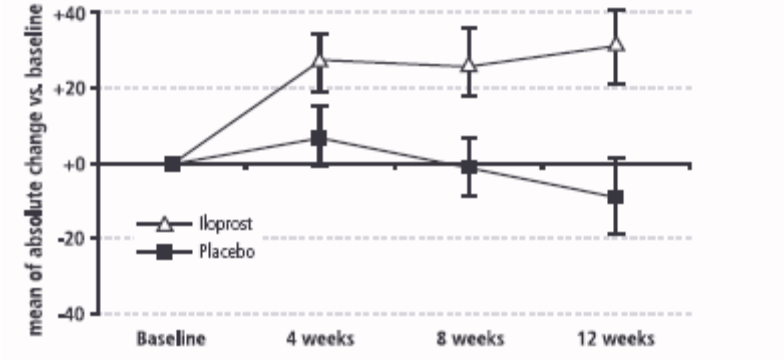
Although effectiveness was seen in the full population (response rates for the primary composite endpoint of 17% and 5%; p=0.007), there was inadequate evidence of benefit in patients with pulmonary hypertension associated with chronic thromboembolic disease (WHO Group IV); the results presented are 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)



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 ± 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)

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

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

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

	Baseline		Mean (± SD) change from baseline at Week 12		
Parameter	**Iloprost**	**Placebo**	**Iloprost**		**Placebo**
			Before Inhalation	**After Inhalation**	
PVR (dyn•s•cm^{-5})	1029 ± 390	1041 ± 493	-9 ± 275 (n=76)	-239 ± 279 (n=70)	+96 ± 323 (n=77)
mPAP (mmHg)	53 ± 12	54 ± 14	-0.2 ± 7.3 (n=93)	-4.6 ± 9.3 (n=90)	-0.1 ± 6.9 (n=82)
CO (L/min)	3.8 ± 1.1	3.8 ± 0.9	+0.1 ± 0.9 (n=91)	+0.5 ± 1.1 (n=89)	-0.2 ± 0.8 (n=80)
SVO_2 (%)	60 ± 8	60±8	-1.1 ± 7.6 (n=72)	+1.8 ± 8.3 (n=70)	-3.2 ± 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 I-neb® 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.

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. Thus patients may want to adjust times of administration to cover planned activities.

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 (Cmax of 45 ng/mL serum), followed by 16 months at 100 mg/kg/day, or in Crl:CD-1®(ICR)BR albino mice dosed orally for up to 24 months at doses of up to 125 mg/kg/day (Cmax of 156 ng/mL serum). The recommended clinical dosage regimen for iloprost (5 mcg) affords a serum Cmax 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 (Cmax of 90 ng/mL), in pregnant rabbits at intravenous dosages of up to 0.5 mg/kg/day (Cmax 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 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

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 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
Prodose® AAD®	2.5 or 5 mcg from two ampules	N/A

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 either the I-neb® AAD® System or the Prodose® AAD®

System medication chamber 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.

Preparation

Ventavis ampules may be opened with an ampule breaker or with a rubber pad.

When using a rubber pad:

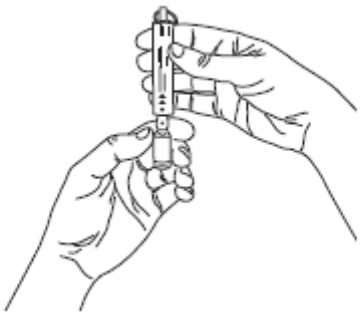
1. With one hand, hold the bottom of the ampule with the blue dot facing away from your body.

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

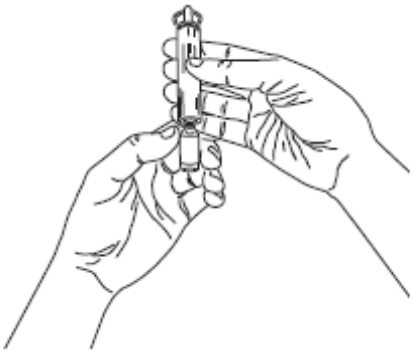
3. Using your thumbs, break open the neck of the ampule by snapping the top towards you and then carefully dispose of the top of the ampule into a sharps bin.

When using an ampule breaker:

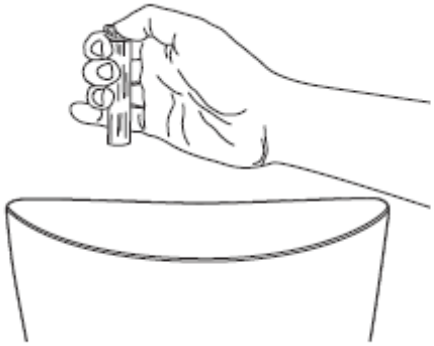
1. Align the blue dot on the Ventavis ampule with the dot on the ampule breaker, if available, and then insert the top of the ampule into the ampule breaker.



2. Gently break open the neck of the ampule by levering away from the dot on the Ventavis ampule to snap off the ampule lid.

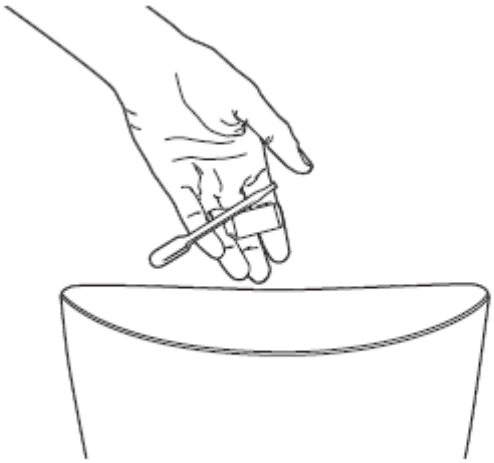


3. Carefully dispose of the top of the ampule into a sharps bin or appropriate storage container.



4. After opening the ampules, use 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. If using the Prodose® AAD® System, two 10mcg/mL ampules need to be added to the medication chamber.

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.



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 Solutionis supplied in cartons of 30 x 1 mL clear glass single-use ampules as follows:

1 mL ampule containing iloprost 10 mcg per mL, carton of 30 (NDC 66215-302-30)

1 mL ampule containing iloprost 20 mcg per mL, carton of 30 (NDC 66215-303-30)

STORAGE

Store at 20 – 25°C (68 – 77°F)

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

[See USP Controlled Room Temperature]

Distributed by:

Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080

August 2009 ACT20090616

PATIENT INFORMATION
Ventavis (ven TAY vis)
(iloprost)
Inhalation Solution

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 Ventavis?

Ventavis is a prescription medicine used to treat adults with certain kinds of severe pulmonary arterial hypertension (PAH), a condition in which blood pressure is too high in the blood vessels between the heart and the lungs. Ventavis may improve your ability to exercise and your symptoms for a short time by lowering your blood pressure and opening up the blood vessels in your lungs.

Ventavis has not been studied in children younger than 18 years old.

What should I tell my doctor before taking Ventavis?

Ventavis may not be right for you. Before taking 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 plan to become pregnant. It is not known if Ventavis can harm your unborn baby. Ventavis should only be used during pregnancy if the benefit to you is worth the possible risk to your baby.
- are breast-feeding. It is not known if Ventavis passes into your breast milk. You and your doctor should decide if you will take Ventavis or breast feed.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Ventavis and other medicines may affect each other causing side effects. Ventavis may affect the way other medicines work, and other medicines may affect how Ventavis works.

Especially tell your doctor if you take:

- medicines used to treat high blood pressure or heart problems
- medicines that lessen blood clotting (warfarin, Coumadin, Jantoven)

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take Ventavis?

See the end of this leaflet for detailed instructions for using Ventavis.

- Take Ventavis exactly as your doctor tells you to take it. Your doctor may change your dose if needed.
- You should not take Ventavis more than every 2 hours. The benefits of Ventavis may not last 2 hours, so you may adjust the times that you use it to cover planned activities.
- Do not drink Ventavis.
- Do not let Ventavis solution come into contact with your skin or eyes. If it does, rinse your skin or eyes with water right away.
- Do not allow other people to be exposed to Ventavis while you are breathing it, especially babies and pregnant women.
- If you take too much Ventavis, you may have a headache, red face, dizziness, nausea, vomiting and diarrhea. If this happens stop taking Ventavis. If your symptoms do not go away, call your doctor or get emergency help right away.

What are the possible side effects of Ventavis?

Ventavis may cause side effects, including feeling dizzy, lightheaded and faint. If you have any of these side effects, you should stand up slowly when you get out of chairs or bed. Tell your doctor if your fainting gets worse during treatment with Ventavis. Your doctor may need to change your dose or 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.

You may have trouble breathing after taking Ventavis because it may cause the muscles around your airway to tighten (bronchospam). Get emergency help right away if you have trouble breathing.

The most common side effects of Ventavis include:

- red face (flushing)
- increased cough
- low blood pressure
- headaches
- nausea
- spasm of your jaw muscles that makes it hard to open your mouth
- fainting

Talk to your doctor if you have any side effect that bothers you or that does not

go away.

These are not all the possible side effects of 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**.**

How should I store Ventavis?

- Store Ventavis between 68°F to 77°F (20°C to 25°C).
- Safely throw away 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 conditions that are not listed in the patient leaflet. 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 you have. It may harm them.

This patient information leaflet summarizes the most important information about Ventavis. If you would like more information about Ventavis talk with your doctor. You can ask your doctor or pharmacist for information about Ventavis that is written for health professionals. For more information go to www.4VENTAVIS.com or call 1-866-ACTELION (1-866-228-3546).

What are the ingredients in Ventavis?

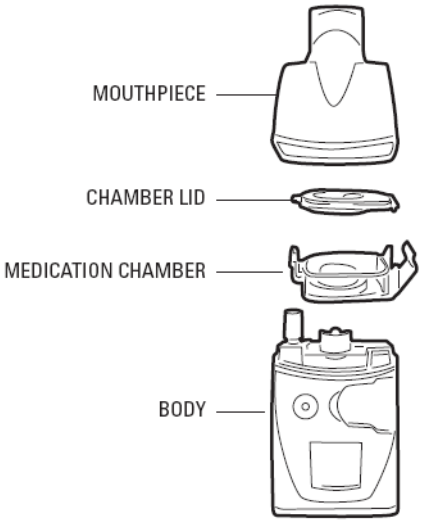
Active ingredient: iloprost
Inactive ingredients: tromethamine, ethanol, sodium chloride, hydrochloric acid for pH adjustment, and water for injection.

Patient Instructions for Using Ventavis

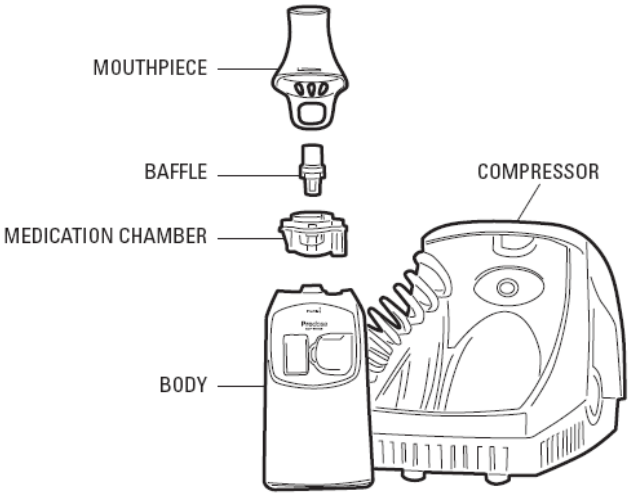
To take Ventavis, you will need to use **either** the Prodose Adaptive Aerosol Delivery (AAD) System **or** the I-neb Adaptive Aerosol Delivery (AAD) System. These systems are used to give you the right dose of Ventavis. You should not use other systems to take Ventavis as other systems may not give you the amount of Ventavis you need.

Do not use Ventavis until your doctor has showed you how to use one of these systems the right way. Make sure you understand all the instructions or ask questions until you do.

I-neb AAD System



Prodose AAD System



If you are using the Prodose System, your doctor will give you 2 dosing discs for it.

Prodose AAD System Dosing Discs

The Prodose dosing discs are white with a red band (2.5 mcg) or purple band (5 mcg) across each disc.

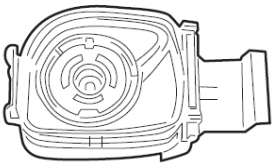
These dosing discs will control the amount of Ventavis you use. **Do not change the dosing disc in your Prodose System without talking to your doctor. Always use all of the contents of 2 ampules (10 microgram per 1 mL only) when using your Prodose System.**

Ventavis Ampule

If you use less than the 2 mL of liquid with the Prodose System it may not give you enough medicine.

If you are using the I-neb System, you will receive two medicine chambers (one with a red latch and one with a purple latch) and two color-matching dosing discs to use with the 10 micrograms per 1 mL of Ventavis.

I-neb System Medication Chamber



You should use the red dosing disc with the red latched medicine chamber (gives you a 2.5 microgram dose). You should use the purple dosing disc with the purple-latched medicine chamber (gives you a 5 microgram dose). **Always use all of the contents of only 1 ampule when using the I-neb System.**

If you are using the I-neb System and usually have long treatment times, your doctor may ask you to switch to a third medicine chamber (one with a yellow latch). The medicine chamber with the yellow latch and matching dosing disc are only for use with the 20 micrograms per 1 mL ampule of Ventavis. You should use the yellow dosing disc with the yellow latched medicine chamber (gives you a 5 microgram dose.).

Do not change the medicine chamber and dosing disc in your I-neb System without talking to your doctor.

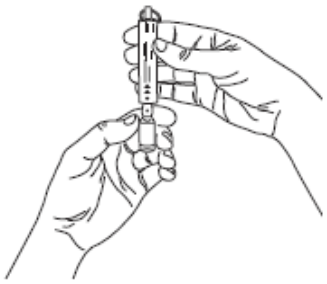
Do not put any medicines other than Ventavis in your Prodose System or I-neb System.

To Use Ventavis:

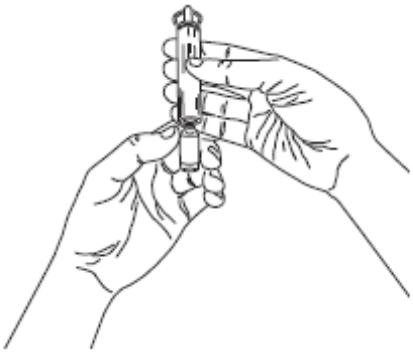
Open the small glass bottle (ampule) of Ventavis by using either an ampule breaker or a rubber pad. Use either the ampule breaker or the rubber pad. You do not need to use both methods to open a Ventavis ampule.

When using an ampule breaker:

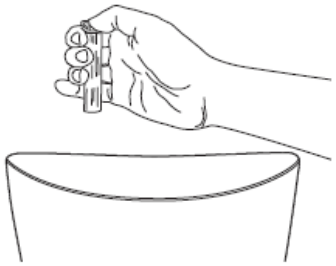
Step 1. Line up the blue dot on the Ventavis ampule with the dot on the ampule breaker, if available, and then insert the top of the ampule into the ampule breaker.



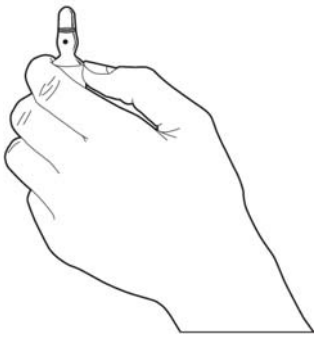
Step 2. Gently break open the neck of the ampule by pushing away from the dot on the Ventavis ampule to snap off the ampule lid.



Step 3. Carefully throw away the top of the ampule into a safe container.



When using a rubber pad:
Step 1. Hold the ampule with the blue dot facing away from your body.

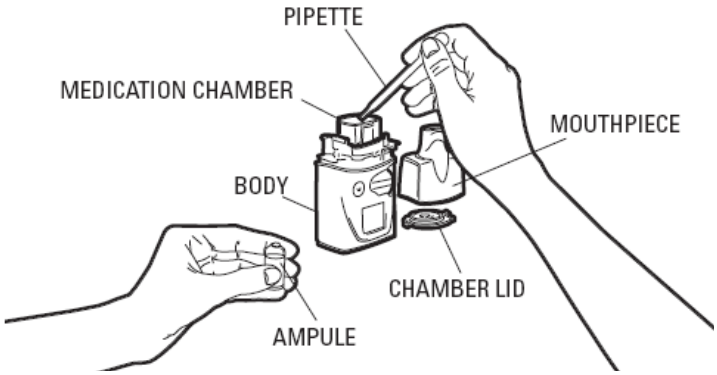


Step 2. Wrap the rubber pad around the ampule to protect yourself from getting cut.

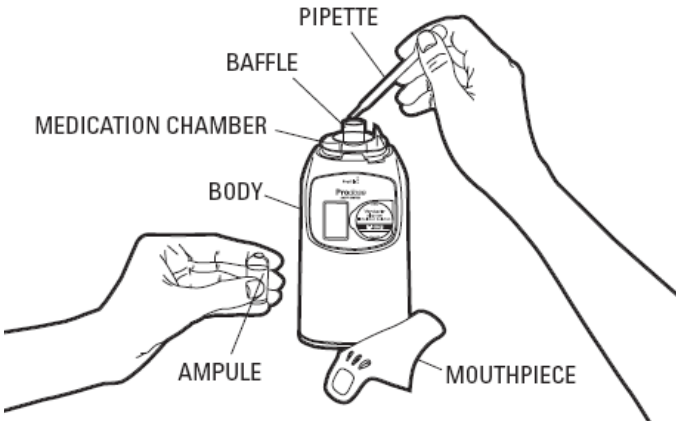
Step 3. Use your thumbs to break open the neck of the ampule by snapping the top toward you.

Step 4. 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 System or the I-neb System medicine chamber. The amount of Ventavis you receive will be controlled by either the dosing disc or the medicine chamber.

I-neb System



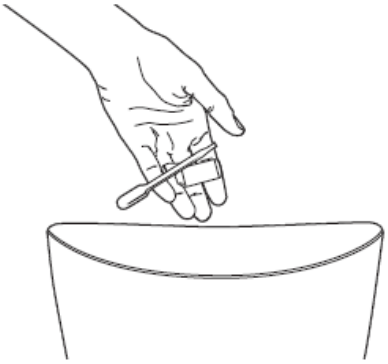
Prodose System



Step 5. Throw away in a safe container the:

- top of the ampule (the ampule lid)
- open ampule

Keep both the ampule and the pipette out of the reach of children.



Step 6. To breathe in your dose of Ventavis, follow the instructions that come with your Prodose System or I-neb System. Each treatment session with Ventavis

lasts about 4 to 10 minutes. Call your doctor if you usually have longer treatment times as your dose may need to be changed.

The Prodose System or I-neb System allows you to stop your treatment for up to ten minutes with no effect on the final dose you get. If your treatment is stopped for more than ten minutes, the Prodose System or I-neb System will reset itself. If that happens, **throw away the solution in the chamber and wait at least two hours before taking your next dose. If you take a second dose right away you could get too much medicine.**

Step 7. Throw away any Ventavis that is left in the medicine chamber after each treatment. Do not use the rest of the Ventavis because it will not give you the right dose.

Step 8. Clean your system after each treatment. Follow the instructions that come with your system.

Step 9. Make sure you have access to a back-up Prodose System or I-neb System to use for Ventavis treatments. This is important if your original system does not work for some reason.

Rx only
Issued August 2009

Actelion Pharmaceuticals US, Inc.
5000 Shoreline Court, Ste. 200
South San Francisco, CA 94080

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-779/S-009

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #2	1. ORGANIZATION	2. NDA NUMBER	
	ONDQA	021779	
3. NAME AND ADDRESS OF APPLICANT		**4. SUPPLEMENT (S)**	
		NUMBER(S)	**DATE(S)**
Actelion Ltd. Innovation Center Gewerbestrasse 16 Allschwil, CH-4123 Switzerland		SCS 009	03/02/2009

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Ventavis	Iloprost	

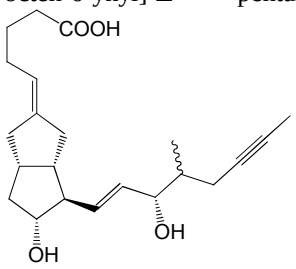
8. SUPPLEMENT PROVIDES FOR:

Introduction of a higher concentration solution (20 µg/mL)

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Pulmonary Arterial Hypertension	RX ✓ OTC	
12. DOSAGE FORM	**13. POTENCY**	
Inhalation Solution	10 µg/mL 20 µg/mL	

14. CHEMICAL NAME AND STRUCTURE

(*E*)-(3a*S*,4*R*,5*R*,6a*S*)-hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H),\Delta}$-pentalenevaleric acid



Chemical Formula: $C_{22}H_{32}O_4$
Molecular Weight: 360.49

15. RECORDS AND REPORTS

16. COMMENTS

A detailed review of this supplement is in Review 1. The EES result for the inspection of the Berlimed facility was pending at the time. The Office of Compliance has provided an acceptable overall recommendation on June 23, 2009 (see attched).

17. CONCLUSION AND RECOMMENDATION

This submission is recommended for approval from the stand point of chemistry, manufacturing and controls.

18. REVIEWERS SIGNATURE	19. DATE COMPLETED
See appended electronic signature sheet	

DISTRIBUTION:	ORIGINAL JACKET	DIVISION FILE	REVIEWER	CSO	BRANCH CHIEF
			Anamitro Banerjee, Ph.D.		J. Vidra, Ph.D.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21779/009	**Sponsor:**	ACTELION PHARM
Org. Code:	110		56 HUCKLEBERRY LANE
Priority:	1P		NORTH ANDOVER, MA 01845
Stamp Date:	02-MAR-2009	**Brand Name:**	VENTAVIS (ILOPROST) INHALATION 10MCG/ML
PDUFA Date:	02-JUL-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	ILOPROST
District Goal:	28-MAY-2009	**Dosage Form:**	(INHALANT)
		Strength:	10 MCG/ML

FDA Contacts:	T. BOUIE	Project Manager	301-796-1649
	N. CHIDAMBARAM	Team Leader	301-796-1339

Overall Recommendation: ACCEPTABLE on 23-JUN-2009 by E. JOHNSON (HFD-320) 301-796-3334

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-APR-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** 3004492234

BERLIMED
POLIG INDUSTRIAL SANTA ROSA

ALCAL DE HENARES MADRID, , SPAIN 28806

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SMALL VOLUME PARENTERAL (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-JUN-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anamitro Banerjee
6/29/2009 10:30:22 AM
CHEMIST

Jim Vidra
6/29/2009 04:54:14 PM
CHEMIST

CHEMIST'S REVIEW #1	1. ORGANIZATION	2. NDA NUMBER	
	ONDQA	021779	
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT (S)	
		NUMBER(S)	DATE(S)
Actelion Ltd. Innovation Center Gewerbestrasse 16 Allschwil, CH-4123 Switzerland		SCS 009	03/02/2009

5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Ventavis	Iloprost	

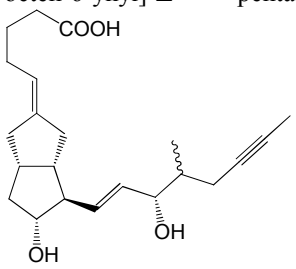
8. SUPPLEMENT PROVIDES FOR:

Introduction of a higher concentration solution (20 µg/mL)

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
Pulmonary Arterial Hypertension	RX ✓ OTC	
12. DOSAGE FORM	**13. POTENCY**	
Inhalation Solution	10 µg/mL 20 µg/mL	

14. CHEMICAL NAME AND STRUCTURE

(*E*)-(3a*S*,4*R*,5*R*,6a*S*)-hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-$\Delta^{2(1H),\Delta}$-pentalenevaleric acid



Chemical Formula: $C_{22}H_{32}O_4$
Molecular Weight: 360.49

15. RECORDS AND REPORTS

16. COMMENTS

See next page

17. CONCLUSION AND RECOMMENDATION

This submission is recommended for approval from the stand point of chemistry, manufacturing and controls subject to the pending EES inspection results.

18. REVIEWERS SIGNATURE	19. DATE COMPLETED
See appended electronic signature sheet	

DISTRIBUTION:	ORIGINAL JACKET	DIVISION FILE	REVIEWER	CSO	BRANCH CHIEF
			Anamitro Banerjee, Ph.D.		J. Vidra, Ph.D.

16 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 21779/009	**Sponsor:**	ACTELION PHARM
Org. Code:	110		56 HUCKLEBERRY LANE
Priority:	1P		NORTH ANDOVER, MA 01845
Stamp Date:	02-MAR-2009	**Brand Name:**	VENTAVIS (ILOPROST) INHALATION 10MCG/ML
PDUFA Date:	02-JUL-2009	**Estab. Name:**	
Action Goal:		**Generic Name:**	ILOPROST
District Goal:	28-MAY-2009	**Dosage Form:**	(INHALANT)
		Strength:	10 MCG/ML

FDA Contacts:	T. BOUIE	Project Manager	301-796-1649
	N. CHIDAMBARAM	Team Leader	301-796-1339

Overall Recommendation:

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-APR-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** 3004492234

BERLIMED
POLIG INDUSTRIAL SANTA ROSA

ALCAL DE HENARES MADRID, , SPAIN 28806

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: SMALL VOLUME PARENTERAL, (b) (4) **OAI Status:** NONE

Last Milestone: INSPECTION SCHEDULED

Milestone Date: 07-MAY-2009

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Anamitro Banerjee
6/19/2009 03:34:28 PM
CHEMIST
EES for BERLIMED is pending as of 06/19/2009. Please do not issue an action letter until the inspection results are received.

Jim Vidra
6/19/2009 03:35:19 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-779/S-009

MICROBIOLOGY REVIEW(S)

Product Quality Microbiology Review

2 JUNE 2009

NDA: 21-779/SCS-009

Drug Product Name
Proprietary: Ventavis
Non-proprietary: iloprost

Review Number: 1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Review Request	Assigned to Reviewer
27 February 2009	2 March 2009	24 March 2009	27 March 2009

Submission History (for amendments only): N/A

Applicant/Sponsor
Name: Actelion Ltd.
Address: Innovation Center, Gewerbestrasse 16, Allschwil, CH-4123, Switzerland
Representative: Frances Dufy-Warren
Telephone: 856-773-5723

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommended for Approval

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Prior Approval Supplement

2. SUBMISSION PROVIDES FOR: New strength for the drug product

3. MANUFACTURING SITE: BerliMed S.A.
Poligono Industrial Santa Rosa
C/Francisco Alonso 7
28806 Alcala de Henares, Madrid
Spain

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile Solution for inhalation in a single-use 1 mL glass vial, 10 mcg/mL and 20 mcg/mL

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Treatment of pulmonary arterial hypertension

B. SUPPORTING/RELATED DOCUMENTS: N/A

C. REMARKS: This was a paper submission (1 volume) in the CTD format. The applicant is proposing the market the drug product at a higher strength as an aid to patients who have difficulty inhaling the full dose (5 mcg) when using the approved 10 mcg/mL product.

filename: N021779S009R1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is (b) (4)

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

Bryan S. Riley, Ph.D.
Senior Review Microbiologist OPS/NDMS

B. Endorsement Block _____

James L. McVey
Team Leader OPS/NDMS

C. CC Block

N/A

Product Quality Microbiology Assessment

The drug product is a single-use sterile aqueous solution in an ampoule for administration via oral inhalation. The drug product was approved as a 10 mcg/mL solution (1 mL/ampoule). The applicant is proposing to add a 20 mcg/mL strength, also in a 1 mL ampoule. The manufacturing process for the 20 mcg/mL product will be identical to that for the approved 10 mcg/mL product. The drug product is (b) (4) .

(b) (4)

ADEQUATE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Bryan Riley
6/8/2009 09:05:44 AM
MICROBIOLOGIST

James McVey
6/8/2009 09:44:33 AM
MICROBIOLOGIST
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-779/S-009

OTHER REVIEW(S)

Regulatory Project Manager's Overview of NDA 21-779/s-009

Application: NDA 21-779/s-009 Ventavis (iloprost) 20 mcg Inhalation Solution

Applicant: Actelion

Letter Date: February 27, 2009

Receipt Date: March 2, 2009

PDUFA Goal Date: July 2, 2009

Amendments: None

Submission Type: Prior approval original CMC supplement (SCS)

Background:

Ventavis (iloprost) 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 a lack of deterioration.

The approved product in dispensed in glass ampules containing 10 mcg/mL iloprost. Patients self-administer the product 6 to 9 times a day using one of two cleared pulmonary drug delivery nebulizers, the I-neb AAD or the Prodose.

- October 3, 2008: Sponsor's meeting request for an alternate concentration
- November 10, 2008: Sponsor's briefing package
- December 9, 2008: FDA premeeting responses
- March 2, 2009: Supplement received and the RPM notified the following parties: CDRH, DMEPA, DRISK, DDMAC, ONDQA, Microbiology, and Clinical

Review:

CDRH: Sugato De

In his review, Mr. De pointed out 3 issues:

Remaining Concerns:

1. Please confirm that the Prodose AAD system will not be intended for the delivery of the newly proposed 20 mcg/mL concentration of Ventavis (iloprost) solution. If the Prodose AAD is intended to deliver the 20 mcg/mL concentration, adequate rationale has not been provided to demonstrate how the in vitro aerosolization data provided for iloprost using the I-Neb AAD system correlates to the Prodose AAD system. In this scenario, it is recommended that the applicant provide an adequate rationale explaining why the particle size distribution and emitted dose data provided utilizing the I-Neb system can be extrapolated to the Prodose AAD system.

2. In the current submission, the applicant has indicated that additional study will be performed in order to verify that new concentration of iloprost is compatible with the I-Neb AAD system parts in terms of adsorption and the extractable/leachable profile. Please provide the results of this testing, including protocols, acceptance criteria, results and conclusions.

3. The applicant has performed comprehensive in vitro testing data for particle size distribution and emitted dose using the newly proposed 20 mcg/mL concentration. It is unclear from the material provided whether the higher concentration of drug may lead to the risk of a precipitate forming in the medication chamber if left for a prolonged period of time, and whether this concentration may lead to changes in the viscosity or surface tension of the drug solution prior to aerosolization. Please discuss whether the 20 mcg/mL concentration affects the conglomeration profile, viscosity or surface tension of the iloprost solution, and whether these changes may affect the particle size and emitted dose from the proposed nebulization device.

With regard to #1 above, the Prodose AAD system will not be intended for the delivery of the newly proposed 20 mcg/mL concentration of Ventavis (iloprost) solution.

We sent the sponsor concerns numbers 2 and 3 above and the sponsor responded as follows:

With regard to #2, the sponsor asked for the additional ongoing study to be submitted as a postmarketing commitment (PMC). CDRH, ONDQA, and the Division agree with the sponsor, therefore, the approval letter will contain the agreed upon commitment to provide the final study report by October 31, 2009.

With regard to #3, the sponsor submitted a response that satisfied the CDRH reviewer's concern.

Regarding the PMCs, the reviewer notes that two separate studies should be performed by the sponsor:

> The first study should be designed to demonstrate that the 20 mcg/mL concentration does not change the extractable/leachable profile in comparison with the the 10 mcg/mL concentration. Please refer to 3.2.P.2.6 (Compatibility) in the February 27, 2009 submission. As discussed in this section, the applicant used the ProDose Nebulizer to evaluate the leachables and extractables using the 10 mcg/mL concentration (July 30, 2004 NDA). Because the new concentration (20 mcg/mL) will only be utilized with the I-Neb AAD Nebulizer, it is recommended that comparative side-by-side bench testing be performed to evaluate the extractables and leachables from the I-Neb AAD Nebulizer from using the 10 mcg/mL and 20 mcg/mL concentrations.
>
> The second study should be designed to evaluate the adsorption of iloprost to the dug contacting components of the I-Neb AAD. Again, we recommend a comparative side-by-side study using the 10 mcg/mL and 20 mcg/mL concentrations.
>
> As mentioned by the ONDQA reviewer, this study would serve to validate the following claim:
>
> "The adsorption results for the 10 mcg/mL solution represent a worst-case scenario since, if there was any adsorption, the proportional change in terms of available dose would be less for the higher concentration (20 mcg/mL) solution than the 10 mcg/mL."

In summary, we are asking the applicant to demonstrate that the leachable/extractable and adsorption profiles of the new device-drug combination (I-Neb AAD with 20 mcg/mL Ventavis) are substantially equivalent to the I-Neb AAD with 20 mcg/mL Ventavis combination.

CMC: Anamitro Banerjee
Recommends approval and the sites were found acceptable on June 23, 2009 – see review for details. He also concurred with the decision to make concern #2 above a PMC.

Microbiology: Bryan Riley
Recommends approval – see review for details.

DMEPA: Laura Pincock
Comments sent to the sponsor via email:

"As part of DMEPA's review of the vial and carton labeling, we compared the currently approved 10 mcg/1 mL packing with the proposed labels and labeling for the new strength 20 mcg/1 mL. We note new references in the proposed labeling that do not appear in the current label and appear to be confusing regarding the 10 mcg/1 mL strength. Although we are not specifically reviewing the 10 mcg/mL labels and labeling, we find this to be problematic in light of the new labeling.

"Specifically, the current 10 mcg/1 mL carton has the statement "Each inhalation session requires one single-use ampule". In the approved PI, it states that "Each inhalation treatment requires one single use ampule" in the Dosage and Administration Section. This is consistent. However, in the new insert labeling, the dose delivery chart refers to "two ampules" for the Prodose AAD (Dosage and Administration Section) and in the Preparation section includes the statement "If using the Prodose AAD System, two 10 mcg/mL ampules need to be added to the medication system".

"It is now inconsistent and confusing to have the 10 mcg/1 mL carton state that "Each inhalation session requires one single-use ampule". Thus the 10 mcg/mL carton label should have that statement removed or there is an increased risk of dosing errors regarding the number of ampules to administer."

Response from sponsor via email:

"We will remove the statement "Each inhalation session requires one single-use ampule" from the 10 mcg/ml carton. We will submit updated 10mcg/ml cartons with the change noted. Please advise if this change should be submitted as CBE-30 or other submission type. It is anticipated that Ventavis 10 mcg/ml with the changed carton would in the commercial supply chain for distribution by January 2010."

Additional comments sent to the sponsor July 1, 2009 via email:

Based upon our Failure Mode and Effects Analysis (FMEA) of the labels and labeling, DMEPA identified several areas of needed improvement. We request you revise your labels and labeling as follows:

A. Ventavis Ampule Label (20 mcg per mL)

1. *Add a statement that the unused portion of Ventavis should be discarded after use (e.g., Discard remaining solution after use).*
2. *Add a prominent statement that this strength (20 mcg per mL) should only be used with the I-neb AAD System.*

B. Ventavis Carton Labeling (30 count of 20 mcg per mL; Proposed Strength)

1. *Increase the prominence of the strength (20 mcg per mL).*
2. *Add a prominent statement that this strength (20 mcg per mL) should only be used with the I-neb AAD System. We suggest adding this statement on the principal display panel.*
3. *Include a statement to the principal display panel of the carton such as "New Concentration" for the first six months of marketing. This statement will inform patients that a second concentration is now marketed and can decrease the potential for confusion between the two concentrations.*

Dr. Pincock's concerns have been adequately addressed by the sponsor; however, with regard to #3 above, the sponsor proposed placing a sticker on the principle display panel of each carton in lieu of printing such information. The sponsor's proposal below appears reasonable to this reviewer and the proposal was forwarded to DMEPA for concurrence.

"Although the Agency prefers printing on the carton, this is not a feasible option as explained below. Therefore the sponsor proposes to use stickers while addressing the concerns of DMEPA/OSE and to address FDA request to label cartons of Ventavis 20 mcg/mL with the words, "New Concentration" for the first 6 months post-launch. The following points provide the actions that will be taken to ensure that the stickers are appropriately placed on the cartons.

"1. Formal vendor agreement: A formal QA agreement, with detailed responsibilities, will be in place with the distribution facility responsible prior to stickers being applied to cartons. In addition, detailed packaging instructions will include a layout of the principal display panel indicating where to place the sticker. For your information, the distribution facility, (b) (4), is FDA registered as a drug repacker / relabeler, and has been inspected by FDA. The last inspection was (b) (4).

"2. Process controls: The stickers will be applied following cGMP. Actelion will ensure that there is adequate training, supervision, documentation (including written procedures and a record of each batch processed), reconciliation, inspection with sign-off, and provision for maintaining retention samples of the stickered carton.

"To further ensure that they will not be placed so as to cover important information, we plan to use transparent stickers.

"The following circumstances, which are specific to this product, have been considered in arriving at our proposal to use stickers.

"a. The "new concentration" stickering program is of short duration and there is a long lead-time to produce and package Ventavis at the manufacturing site in Spain
- It is difficult to accurately predict demand for the product over the span of 6 months post-launch
b. Ventavis is not a high volume product which makes it amenable to a short duration, stickering program vs preprinted cartons."

In this reviewer's opinion, regardless of the decision of use of a sticker, this issue should not preclude approval of the new strength.

DRISK: Robin Duer
Ms. Duer reviewed the patient package insert and instructions for use. She recommended several revisions to the labeling. Her recommendations were reviewed by the Division, communicated to the sponsor, and the sponsor subsequently revised both the PPI and IFU.

Clinical: Maryann Gordon
No formal review, however, Dr. Gordon reviewed the labeling and concurred with the final version.

DDMAC: No comments.

LABELING REVIEW

Changes in the package insert are as follows:

DESCRIPTION: This section is being revised to add the description for the 1 mL ampules containing Ventavis (iloprost) 20 mcg/mL.

FROM

> 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.

TO

> Ventavis (iloprost) Inhalation Solution is a clear, colorless, sterile solution containing 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 1 mL single-use glass ampules containing either 10 mcg/mL or 20 mcg/mL.
>
> For the 10 mcg/mL solution, one mL of the 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.
>
> For the 20 mcg/mL solution, each mL of the solution contains 0.02 mg iloprost, 1.62 mg ethanol, 0.242 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.76 mg hydrochloric acid (for pH adjustment to 8.4) in water for injection.

PRECAUTIONS/Information for Patients: This section is being revised to add the following sentence to the last paragraph: "Thus patients may want to adjust times of administration to cover planned activities."

FROM

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.

TO

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. Thus patients may want to adjust times of administration to cover planned activities.

DOSAGE AND ADMINISTRATION: This section is being revised to:

- Add a separate set of instructions for opening sealed glass ampules using an ampule breaker (current instructions are for opening with the supplied rubber pad). These instruction are consistent with the instructions provided by the manufacturer of the ampule breaker.
- Provide instructions for the safe disposal of the top of the ampule into a sharps container.
- Add the instruction to use 2 x 1 mL ampules (instead of 1 x 2 mL ampule) for the Prodose AAD System now that the 2 mL ampules are no longer available.

FROM

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

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.

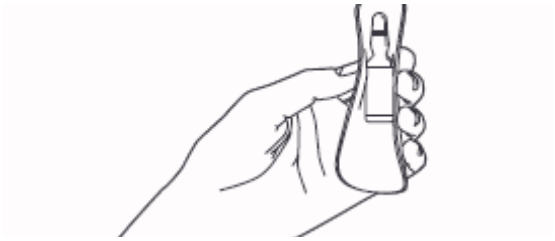
Each inhalation treatment requires one single-use ampule.

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.

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.

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.

TO

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
Prodose® AAD®	2.5 or 5 mcg from two ampules	N/A

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 either the I-neb® AAD® System or the Prodose® AAD® System medication chamber 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.

Preparation

Ventavis ampules may be opened with an ampule breaker or with a rubber pad.

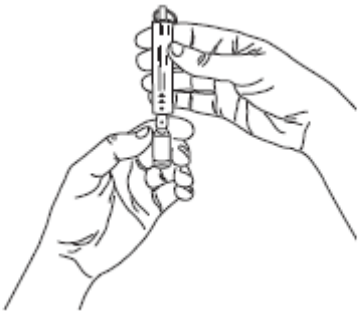
When using a rubber pad:

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

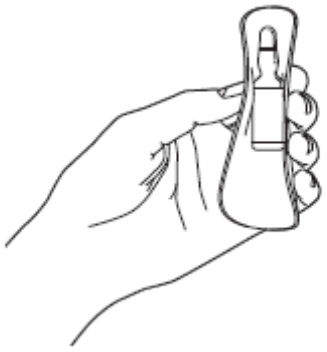
2. With the other hand, wrap the included rubber pad around the entire ampule.

When using an ampule breaker:

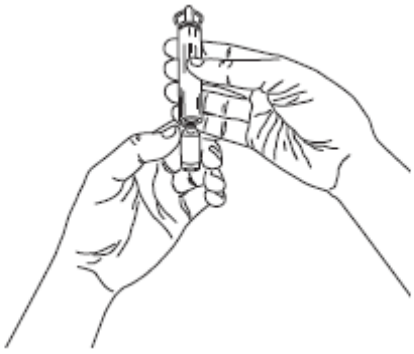
1. Align the blue dot on the Ventavis ampule with the dot on the ampule breaker, if available, and then insert the top of the ampule into the ampule breaker.



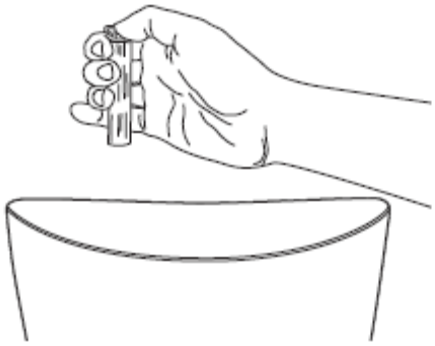
2. Gently break open the neck of the ampule by levering away from the dot on the Ventavis ampule to snap off the ampule lid.



3. Using your thumbs, break open the neck of the ampule by snapping the top towards you and then carefully dispose of the top of the ampule into a sharps bin.

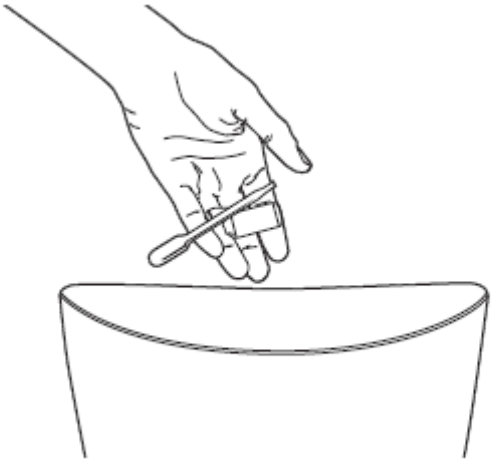


3. Carefully dispose of the top of the ampule into a sharps bin or appropriate storage container.



4. After opening the ampules, use 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. If using the Prodose® AAD® System, two 10mcg/mL ampules need to be added to the medication chamber.

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.



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.

HOW SUPPLIED: This section is being revised to add the description for 1 mL ampules containing Ventavis (iloprost) 20 mcg/mL, cartons of 30, with the corresponding NDC number.

FROM

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

TO

Ventavis (iloprost) Inhalation Solutionis supplied in cartons of 30 x 1 mL clear glass single-use ampules as follows:

1 mL ampule containing iloprost 10 mcg per mL, carton of 30 (NDC 66215-302-30)

1 mL ampule containing iloprost 20 mcg per mL, carton of 30 (NDC 66215-303-30)

Also, changes to the patient information leaflet have been revised in several sections to reflect the addition of a new strength of Ventavis (iloprost), to ensure consistency in content between the patient and prescriber labeling text, and to improve overall readability.

Conclusion:

All concerns have been addressed and an approval letter with a CMC PMC will be drafted for Dr. Stockbridge's signature. In the letter, we will request that the sponsor submit "**SPL for approved NDA 21-779/S-009**" within 14 days of the date of the approval letter.

Dan Brum, Pharm.D.
Regulatory Health Project Manager

Reviewed on 6/18/09
Revised 6/29/09
Revised 8/4/09, 8/5/09, 8/7/09

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANIEL BRUM
08/07/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES **M E M O R A N D U M**

Food and Drug Administration
Anesthesia and Respiratory Devices Branch
Division of Anesthesiology, General Hospital, Infection Control and Dental Device
Office of Device Evaluation
9200 Corporate Boulevard
Rockville, MD 20850

NDA 22-779 – Regulatory Device Review

Date: June 10, 2009
To: Daniel Brum, Regulatory Project Manager (OND/ODEI/DCRP)
From: Sugato De, Biomedical Engineer (ODE/DAGID/ARDB)

Applicant: Actelion Clinical Research, Inc.
Device Name: Ventavis Inhalation Solution
Indication: Pulmonary Hypertension

A. Background

In NDA 22-779, Actelion Clinical Research, Inc. has proposed a combination product intended for the delivery of a novel 20 mcg/ml concentration of Ventavis. On December 30, 2004, Ventavis Inhalation Solution was approved for the treatment of pulmonary arterial hypertension. In controlled trials, the drug was shown to improve a composite endpoint consisting of exercise tolerance, symptoms, and lack of deterioration. The inhalable form of Ventavis has the advantage of selective deposition in the lungs to help reduce systemic pharmacologic effects.

The approved product is dispensed in glass ampules containing 10 mcg/ml iloprost. Patients self-administer the product six to nine times daily using one of two approved pulmonary drug delivery devices, the I-Neb AAD (Adaptive Aerosol Delivery) System or the Prodose AAD System. The device is designed to delivery the approved dose of either 2.5 or 5 mcg iloprost ex-mouthpiece, depending on the selection of medication chambers with volumes of 0.25 ml or 0.5 ml, respectively. The maximum daily dose evaluated in previously performed clinical trials is 45 mcg.

Actelion is filing the current supplemental NDA for the introduction of a higher concentration solution (Ventavis 20 mcg/ml) for inhalation. It will be offered as an alternative delivery option for patients who are receiving the 5 mcg dose but have difficulty inhaling the full dose with the current 10 mcg/ml formulation. This does not involve a change in dose, inhalation device, device components, dosing regiment, or route of administration.

Recommendations**:**

- The in vitro data demonstrates that the I-Neb AAD system can deliver a comparable aerosolized dose of 5.0 mcg iloprost with a 20 mcg/mL iloprost solution for inhalation as with a 10 mcg/mL iloprost solution.

- If the Prodose AAD is intended to deliver the 20 mcg/mL concentration, adequate rationale has not been provided to demonstrate how the in vitro aerosolization data provided for iloprost using the I-Neb AAD system correlates to the Prodose AAD system.

- The applicant has indicated that additional study will be performed in order to verify that new concentration of iloprost is compatible with the I-Neb AAD system parts in terms of adsorption and the extractable/leachable profile. The results of this testing, including protocols, acceptance criteria, results and conclusions are required for review.

- It is recommended that the applicant discuss whether the 20 mcg/mL concentration affects the conglomeration profile, viscosity or surface tension of the iloprost solution, and whether these changes may affect the particle size and emitted dose from the proposed nebulization device.\

B. Combination Device Description

Ventavis (iloprost) Inhalation Solution is a clear, colorless, sterile solution containing 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 1 mL single-use glass ampules containing either 10 mcg/1 mL or 20 mcg/1 mL.

For the 10 mcg/1mL solution, one 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). For the 20 mcg/1mL solution, one mL of the aqueous solution contains 0.02 mg iloprost, 1.62 mg ethanol, 0.242 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.76 mg hydrochloric acid (for pH adjustment to 8.4).

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).

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 the nebulizer being utilized.

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

	Delivered Dose From Ampule Of:	
Nebulizer	10 mcg/1mL	20 mcg/1mL
I-neb® AAD®	2.5-5 mcg from one ampule	5 mcg from one ampule
Prodose® AAD®	2.5-5 mcg from two ampules	N/A

The 20 mcg/1mL 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/1mL 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 either the I-Neb AAD System or the Prodose AAD System medication chamber 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.

C. In Vitro Aerosol Studies

The in-vitro data provided in the current supplement adequate demonstrates that the I-Neb AAD system can deliver a comparable aerosolized dose of 5.0 mcg iloprost with a 20 mcg/mL iloprost solution for inhalation as with 10 mcg/mL iloprost solution for inhalation. This result was demonstrated using validated analytical methods and testing previously applied in previous submissions for Ventavis.

The comparison and similarity between the aerosolized dose of 5.0 mcg with a 10 mcg/mL from a purple-latched medication chamber and with a 20 mcg/mL from a yellow latched medication chamber was demonstrated in terms of emitted dose and particle size distribution. This submission supports the inclusion of the 20 mcg/mL iloprost solution and yellow-latch medication chamber in the labeling and approved package insert for the administration of Ventavis aerosol to patients with pulmonary arterial hypertension. There will be no change to the currently approved I-Neb AAD system medication chambers with red and purple latches that deliver the 2.5 mcg and 5.0 mcg doses, respectively, with the 10 mcg/mL solution. To deliver the 5.0 mcg dose with the 20 mcg/mL solution, the sponsor will provide a separate medication chamber with a yellow latch and a color-matching power 6 disc.

The bench testing data studies provided in the current submission were conducted at the laboratories of (b) (4) and are replicated from previous studies conducted at (b) (4) Throughout these studies, iloprost concentrations were quantified using a validated HPLC method.

Particle Size Distribution Analysis:

(b) (4)

The particle size distribution analysis using the 20 mcg/mL concentration demonstrates substantial equivalence in terms of reproducibility, MMAD and fine particle fraction in comparison with the 10 mcg/mL dose.

Emitted Dose:

(b) (4)

(b) (4)

The emitted dose data demonstrates adequate similarity and reproducibility and demonstrates that the I-Neb AAD system can accurately delivery a 5.0 mcg dose with the 20 mcg/mL solution and the new yellow-latched medication chamber.

D. Device Compatibility

A compatibility study was performed between Ventavis 10 mcg/mL and the Prodose Nebulizer. The results show that iloprost solution is compatible in terms of acceptable levels of leachables and lack of significant adsorption of iloprost to the product contact component.

These data also support the use of the I-Neb AAD system since the product contact materials are identical to those used for the Prodose AAD system (i.e. (b) (4)).

Since the compatibility data generated with the lower concentration solution represents the worst-case scenario, it can be extrapolated to the higher concentration solution of 20 mcg/mL. The new concentration of iloprost is expected to be compatible with the I-Neb AAD system parts in terms of adsorption. However, Actelion has agreed to perform additional studies to confirm that the 20 mcg/mL concentration dose not change the extractable/leachable profile.

E. Review Conclusions

The in vitro data demonstrates that the I-Neb AAD system can deliver a comparable aerosolized dose of 5.0 mcg iloprost with a 20 mcg/mL iloprost solution for inhalation as with a 10 mcg/mL iloprost solution. This result was demonstrated using validated analytical methods and testing that were shown to delivery equivalent results to those already described in the April 29, 2005 NDA submission for the 10 mcg/mL concentration dose. The comparison and similarity between the aerosolized dose of 5.0 mcg with a 10 mcg/mL concentration from a purple-latched medication chamber and with 20 mcg/mL from a yellow-latched medication chamber was demonstrated in terms of emitted dose and particle size distribution. This submission supports the inclusion of the 20 mcg/mL iloprost solution and yellow-latched medication chamber in the labeling and approved package insert for the administration of Ventavis aerosol to patients with pulmonary arterial hypertension. There will be no change to the currently approved I-Neb AAD system medication chambers with the red and purple latches that deliver the 2.5 mcg and 5.0 mcg doses respectively with the 10 mcg/mL solution. To deliver the 5.0 mcg dose with the 20 mcg/mL solution, the applicant will provide a separate newly-designed medication chamber with a yellow latch and color matching power 6 disks.

Remaining Concerns:

1. Please confirm that the Prodose AAD system will not be intended for the delivery of the newly proposed 20 mcg/mL concentration of Ventavis (iloprost) solution. If the Prodose AAD is intended to deliver the 20 mcg/mL concentration, adequate rationale has not been provided to demonstrate how the in vitro aerosolization data provided for iloprost using the I-Neb AAD system correlates to the Prodose AAD system. In this scenario, it is recommended that the applicant provide an adequate rationale explaining why the particle size distribution and emitted dose data provided utilizing the I-Neb system can be extrapolated to the Prodose AAD system.

2. In the current submission, the applicant has indicated that additional study will be performed in order to verify that new concentration of iloprost is compatible with the I-Neb AAD system parts in terms of adsorption and the extractable/leachable profile. Please provide the results of this testing, including protocols, acceptance criteria, results and conclusions.

3. The applicant has performed comprehensive in vitro testing data for particle size distribution and emitted dose using the newly proposed 20 mcg/mL concentration. It is unclear from the material provided whether the higher concentration of drug may lead to the risk of a precipitate forming in the medication chamber if left for a prolonged period of time, and whether this concentration may lead to changes in the viscosity or surface tension of the drug solution prior to aerosolization. Please discuss whether the 20 mcg/mL concentration affects the conglomeration profile, viscosity or surface tension of the iloprost solution, and whether these changes may affect the particle size and emitted dose from the proposed nebulization device.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dan Brum
7/21/2009 02:38:32 PM
CSO
Placing CDRH consult/review in DFS on behalf of Sugato De

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 30, 2009
To:	Norman Stockbridge, M.D., Director Division of Cardiovascular and Renal Products
Through:	Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Laura Pincock, PharmD, Acting Team Leader Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Ventavis (Iloprost) Inhalation Solution 20 mcg per mL
Application Type/Number:	NDA # 21-779/S-009
Applicant:	Actelion Ltd.
OSE RCM #:	2009-449

CONTENTS

EXECUTIVE SUMMARY

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed ampule label and carton labeling of this new strength introduces vulnerability to confusion that could lead to medication errors. DMEPA compared the labels and labeling of the currently approved strength (10 mcg per mL) to the proposed labels and labeling of the proposed strength (20 mcg per mL). We recommended improvements to increase the prominence, consistency, and clarity of important information on the Ventavis labels and labeling. These risks can be addressed and mitigated prior to drug approval. We note that use of the specialty pharmacies for distribution helps ensure that patients are trained on the appropriate use of Ventavis ampules with the delivery device systems. We provide our recommendations in Sections 3.5 and 3.6.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Cardiovascular and Renal Products for assessment of the container label, carton, and insert labeling for the new strength (20 mcg per mL) of Ventavis inhalation solution to identify areas that could lead to medication errors.

1.2 PRODUCT INFORMATION

Ventavis is currently approved for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms. The approved insert labeling states that Ventavis inhalation solution is currently marketed in the strength of 10 mcg per 1 mL in two sizes: 1 mL and 2 mL ampules. This supplement is for a new strength of Ventavis of 20 mcg per 1 mL. Both strengths will be marketed in 1 mL ampules. According to the Applicant, the 2 mL ampule of 10 mcg/2 mL is no longer available and all stock is expired. The Applicant also stated that the Prodose AAD System is no longer manufactured and limited stock of the nebulizer has been maintained for current users until they are depleted.

Ventavis is intended for inhalation with either of two pulmonary drug delivery devices: the I-neb AAD System or the Prodose AAD System. The current strength (10 mcg/1 mL can be used with either device, however, the new strength (20 mcg/1 mL) can only be used with the I-neb AAD System. The first inhaled dose should be 2.5 mcg (as delivered via the mouthpiece). If this dose is well tolerated, dosing should be increased to 5 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 every 2 hours) during waking hours, according to individual need and tolerability.

Ventavis will be supplied in two strengths: 10 mcg per 1 mL and 20 mcg per 1 mL.

- The 10 mcg per 1 mL (currently marketed) concentration is for use with either the I-neb AAD System or the Prodose AAD System (now discontinued). When used with the I-neb AAD System, the 10 mcg/mL delivers a dose of either 2.5 mcg or 5 mcg at the mouthpiece. When used with the Prodose AAD System, it is necessary (due to design of the device) to use the contents of two ampules to deliver a dose of either 2.5 mcg or 5 mcg.

- The 20 mcg per 1 mL (proposed) concentration is intended for use only with the I-neb AAD System to deliver a dose of 5 mcg at the mouthpiece. The 20 mcg per mL concentration is intended for patients who are maintained at a 5 mcg dose and who have repeatedly experienced extended treatment times.

Patients receiving Ventavis should be advised to use the drug only as prescribed with the specified drug delivery devices. Patients should be trained in proper administration techniques including dosing frequency, ampule dispensing, the System operation, and equipment cleaning. We note that Ventavis is distributed via specialty pharmacies with restricted distribution and according to the Applicant, all patients are trained on the appropriate use of Ventavis with their nebulizer system.

Ventavis should be stored at Controlled Room Temperature with excursions permitted.

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the ampule label, carton labeling, and insert labeling submitted as part of the February 27, 2009 submission (see Appendices A and B) for the new strength of 20 mcg per 1 mL. The approved labels and labeling for the currently marketed strength (10 mcg per 1 mL) are in Appendices C and D.

2.1 AERS SELECTION OF MEDICATION ERROR CASES

Ventavis is currently marketed in the United States in the 10 mcg per 1 mL strength. Therefore, DMEPA performed a search of the FDA AERS database for medication errors involving the labels and labeling of Ventavis.

The MedRA High Level Group Term (HLGT) "Medication Errors" and Preferred Term (PT) "Pharmaceutical product complaint" were used as search criteria. The search criteria used for Products were active ingredient "ilopros%", trade name "Ventav%" and verbatim substance search "Ventavi%".

3 DISCUSSION AND RECOMMENDATIONS

3.1 AERS SELECTION OF CASES

DMEPA notes that Ventavis is currently marketed with the strength of 10 mcg per mL in two vial sizes of 1 mL and 2 mL, although the 2 mL strength has been discontinued and all stocks are expired. Therefore, as part of the label and labeling review we conducted a search of the FDA AERS database for the product Ventavis to determine if there are any problem areas that may be applicable to this review.

The AERS search performed on June 8, 2009, yielded 11 reports. After eliminating duplicate reports and reports that did not contain a medication error relevant to this review, only one case remained. The case (ISR 5507346) dated October 30, 2007 was reported to Medwatch by the Manufacturer. A female school nurse, who was preparing a dose, reported having difficulty snapping the ampule and cut her finger on the broken ampule, which began to bleed. A few minutes later she developed a headache and tingly feet. The events completely resolved by the next day. Therefore, the AERS search identified this one error with the currently marketed Ventavis product which is packaged in glass ampules. Although this medication error is not directly related to our review,

DMEPA believes it is important to note that patients and caregivers can have difficulty opening the glass ampules, therefore it is important to include clear directions on how to open the ampules in the patient labeling (see 3.4.2).

3.2 ADDITION OF NEW STRENGTH (20 MCG PER ML)

This supplement is for a new strength of Ventavis of 20 mcg per 1 mL. The proposed 20 mcg per mL concentration is intended for use only with the I-neb AAD System to deliver a dose of 5 mcg at the mouthpiece. The Applicant states that the 20 mcg per mL concentration is intended for patients who are maintained at a 5 mcg dose and who have repeatedly experienced extended treatment times. Additionally, the Applicant states that transitioning patients to the 20 mcg per mL concentration with the I-neb System will decrease treatment times to help maintain patient compliance. DMEPA notes that addition of an additional strength can provide the opportunity for medication errors, however it appears in this case, it is reasonable that the additional strength be approved.

3.3 VENTAVIS AND DELIVERY DEVICE ISSUES

The new strength can only be used with the I-neb AAD System, and the currently marketed strength can be used with either the Prodose AAD System or the I-neb AAD System. This difference provides opportunity for medication errors. DMEPA learned that Ventavis is distributed via specialty pharmacies and all patients are trained on the appropriate use of Ventavis ampules with either the Prodose AAD System or the I-neb AAD System. As the Prodose AAD System is no longer manufactured, existing supplies of the device are maintained for those patients who have not been able to switch successfully to the I-neb AAD System. Thus, all new patients are started on the I-neb AAD System and will receive training on the appropriate use of this nebulizer. This individual training on the appropriate use of Ventavis ampules with the I-neb AAD System should help mitigate the potential for improper use and decrease the potential for medication errors associated with preparation of the dose, use of the correct strength, and use of the device itself.

3.4 VENTAVIS LABELS AND LABELING

DMEPA evaluated the currently approved 10 mcg/1 mL ampule's labels and labeling as part of our safety review of the 20 mcg/1 mL labels and labeling. We note new recommendations in the proposed labeling that do not appear in the current approved label. This difference introduces confusion regarding the 10 mcg/mL strength.

Specifically, the current 10 mcg/mL carton has the statement "Each inhalation session requires one single-use ampule". In the approved PI, the Dosage and Administration section states that "Each inhalation treatment requires one single use ampule". These two statements are consistent with each other. However, in the proposed insert labeling for the new 20 mg/mL strength, in the Dosage and Administration section, the dose delivery chart refers to the need for "two ampules" for the Prodose AAD and includes the statement in the Preparations section "If using the Prodose AAD System, two 10 mcg/mL ampules need to be added to the medication system".

The reference to the use of two ampules for the Prodose AAD System appears to be a new recommendation. It is now inconsistent and confusing to have the 10 mcg/1 mL carton state that "Each inhalation session requires one single-use ampule" if the

recommendations for the Prodose AAD System are to use 2 ampules. Thus, the 10 mcg/mL carton label should have that statement removed or there is an increased risk of dosing errors regarding the number of ampules to administer. This discrepancy was communicated to the Applicant and they have agreed to remove this statement in an email to Dan Brum, dated June 17, 2009.

Additionally, our evaluation noted areas where information on the container labels, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.4 *Comments to the Division* for discussion during the review team's label and labeling meetings. These revisions were also provided to the Applicant and revisions were made accordingly. Section 3.5 *Comments to the Applicant* contains our recommendations for the container label and carton labeling.

3.5 COMMENTS TO THE DIVISION

Per our request, the Applicant has made all requested revisions that appear below.

1. Remove all trailing zeroes in numbers (e.g., use 5 micrograms rather than 5.0 micrograms), because they can result in ten-fold overdoses. We note the use of "5.0 mcg" in both the PI and PPI.
2. For the "To Use Ventavis" section (or called the "Preparation" section in the PPI), the directions for both methods of opening the ampule should not be communicated side-by-side. We prefer communicating one method first, then the other. Otherwise, it may be confusing if patients switch from one set of directions to the other, leading to a preparation error or harm such as cutting themself with a broken ampule.
3. For the currently marketed carton labeling (10 mcg per mL), remove the statement that "Each inhalation session requires one single-use ampule" since it is inconsistent with the newly added recommendation in the insert labeling to use two ampules in the Prodose AAD System.

3.6 COMMENTS TO THE APPLICANT

Based upon our Failure Mode and Effects Analysis (FMEA) of the labels and labeling, DMEPA identified several areas of needed improvement. We request you revise your labels and labeling as follows:

A. Ventavis Ampule Label (20 mcg per mL)

1. Add a statement that the unused portion of Ventavis should be discarded after use (e.g., Discard remaining solution after use).
2. Add a prominent statement that this strength (20 mcg per mL) should only be used with the I-neb AAD System.

B. Ventavis Carton Labeling (30 count of 20 mcg per mL; Proposed Strength)

1. Increase the prominence of the strength (20 mcg per mL).
2. Add a prominent statement that this strength (20 mcg per mL) should only be used with the I-neb AAD System. We suggest adding this statement on the principal display panel.

3. Include a statement to the principal display panel of the carton such as “New Concentration” for the first six months of marketing. This statement will inform patients that a second concentration is now marketed and can decrease the potential for confusion between the two concentrations.

REFERENCES

Adverse Events Reporting System (AERS)

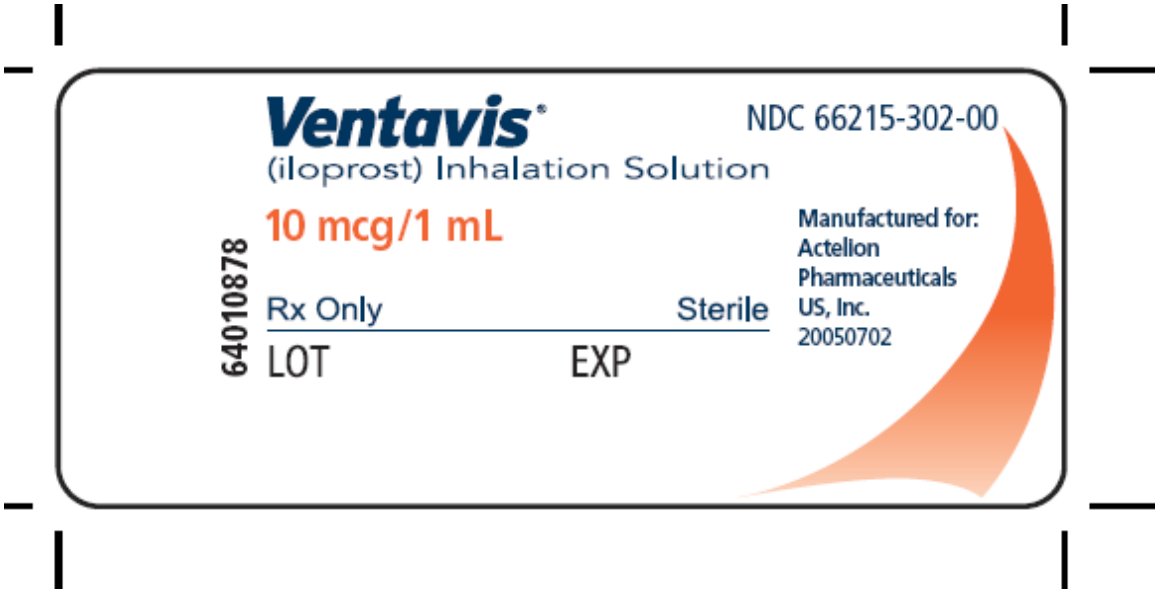
AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPENDICES

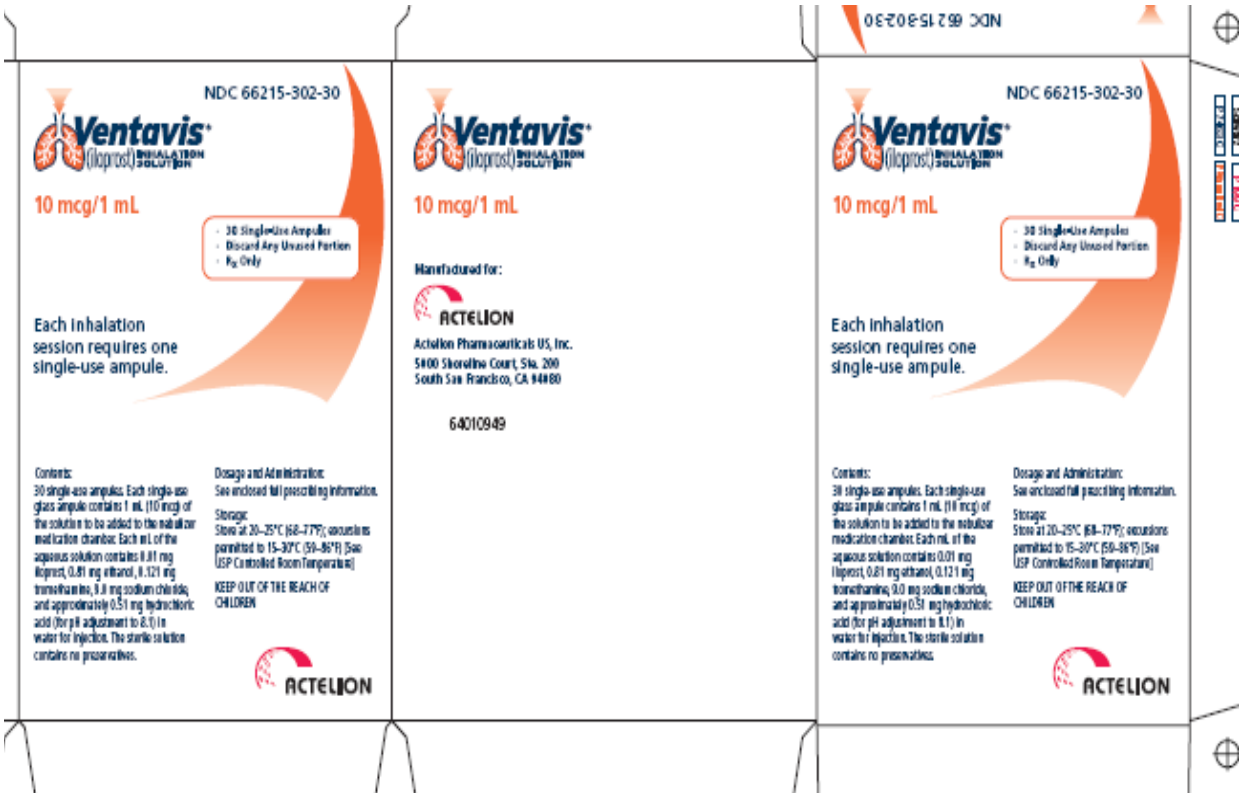
<u>Appendix A:</u> Ventavis Ampule Label (20 mcg per 1 mL)

Appendix B: Ventavis Carton Labeling (20 mcg per 1 mL, 30 count; Proposed Strength)

<u>Appendix C:</u> Ventavis Ampule Label (10 mcg/1 mL; Currently Marketed Strength)



<u>Appendix D:</u> Ventavis Carton Labeling (10 mcg/1 mL; Currently Marketed Strength)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Laura Pincock
6/30/2009 12:07:34 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/30/2009 12:54:42 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 8, 2009
To:	Norman Stockbridge, MD, Director **Division of Cardiovascular and Renal Products (DCRP)**
Through:	Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	Robin Duer, RN, MBA Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling, Patient Package Insert and Instructions for Use
Drug Name(s):	Ventavis® (iloprost) Inhalation Solution
Application Type/Number:	NDA 21-779
Submission Number:	009
Applicant/sponsor:	Actelion Pharmaceuticals US, Inc.
OSE RCM #:	2009-448

INTRODUCTION

NDA 21-779 was approved on December 29, 2004. On February 27, 2009, the Applicant submitted S-009, a chemistry supplement with revised labeling which provided for the addition of a 20 mcg/1 mL concentration for Ventavis® Inhalation Solution. Revised patient labeling in the form of a Patient Package Insert (PPI) and Instructions for Use (IFU) was also included in the submission. On March 11, 2009 the Division of Cardiovascular and Renal Products (DCRP) requested that the Division of Risk Management (DRISK) provide DCRP with a review of the submitted patient labeling. This review is written in response to that request.

1 MATERIAL REVIEWED

- Ventavis Inhalation Solution Patient Package Insert (PPI) dated February 27, 2009
- Ventavis Inhalation Solution Instructions for Use (IFU) dated February 27, 2009
- Ventavis Inhalation Solution Package Insert (PI) dated May 29, 2009

2 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The draft PPI and IFU submitted by the Applicant has a Flesch Kinkaid grade level of 8.7, and a Flesch Reading Ease score of 59%. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). Our revised PPI/IFU has a Flesch Kinkaid grade level of 7.3, and a Flesch Reading Ease score of 66%.

In our review of the PPI and IFU we have:

- simplified wording and clarified concepts where possible,
- ensured that the PPI and IFU are consistent with the PI,
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

Additionally, in 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI and IFU. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised PPI and Patient Instructions for Use. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the PPI and IFU.

3 CONCLUSIONS AND RECOMMENDATIONS

In both the PPI and IFU we

- deleted redundant information that appears in both documents
- shortened the name of the two systems used to inhale Ventavis for easier readability

In the PPI we

(b) (4)

In the IFU we

Please let us know if you have any questions.

21 Pages of Draft Labeling have been Withheld in Full as b4 (CCI) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robin E Duer
6/8/2009 10:40:52 AM
DRUG SAFETY OFFICE REVIEWER

Mary Dempsey said the memo was fine.

Jodi Duckhorn
6/8/2009 11:55:07 AM
DRUG SAFETY OFFICE REVIEWER