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.

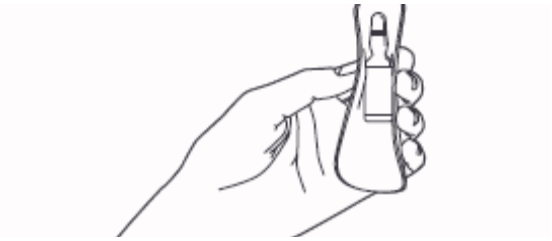
Each inhalation treatment requires one single-use ampule.

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.

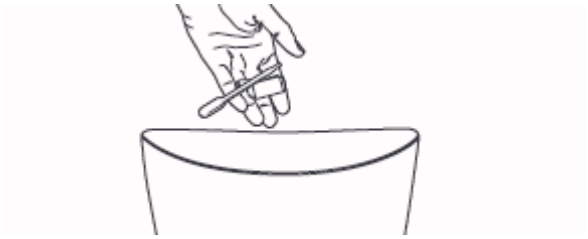
2. With the other hand, wrap the included rubber pad round the entire ampule.



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:

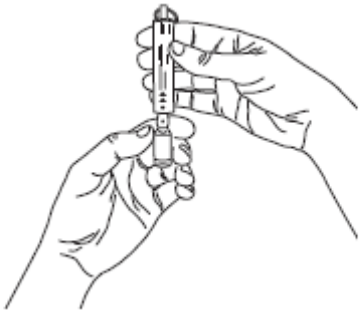
1. With one hand, hold the bottom of the ampule with the blue dot facing away from your body.

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

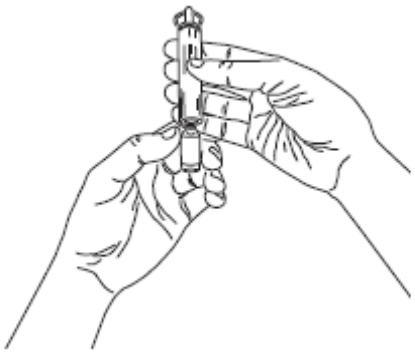
3. Using your thumbs, break open the neck of the ampule by snapping the top towards you and then carefully dispose of the top of the ampule into a sharps bin.

When using an ampule breaker:

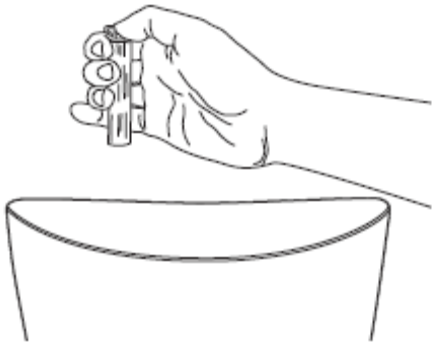
1. Align the blue dot on the Ventavis ampule with the dot on the ampule breaker, if available, and then insert the top of the ampule into the ampule breaker.



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