DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021779/S-014

SUPPLEMENT APPROVAL

Actelion
Attention: Frances Duffy-Warren, PhD
Vice-President, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Duffy-Warren:

Please refer to your Supplemental New Drug Application (sNDA) dated and received June 5, 2013, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ventavis (iloprost) Inhalation Solution, 10 mcg/mL and 20 mcg/mL.

This supplemental new drug application provides for labeling revised as follows (additions are marked as underlined text and deletions are marked as ~~strikethrough text~~):

1. In **HIGHLIGHTS/DOSAGE AND ADMINISTRATION**, the following text was deleted:

   Ventavis is intended to be inhaled using ~~either of two pulmonary drug devices~~ the I-neb® AAD® System ~~or the Prodose® ADD System®.~~ Patients should receive 6 to 9 doses (inhalations) per day (minimum of 2 hours between doses during waking hours) as follows:
   - Starting dose: 2.5 mcg (2.1).
   - Uptitrate to 5 mcg if 2.5 mcg is well tolerated (2.1).
   - Maintenance dose: 5 mcg (2.1).

	Delivered dose from ampule of :	
Nebulizer	10 mcg/mL	20 mcg/mL
I-neb® AAD®	2.5 or 5 mcg from one ampule	5 mcg from one ampule
~~Prodose® ADD®~~	~~2.5 or 5 mcg from two ampules~~	~~N/A~~

2. Under **DOSAGE AND ADMINISTRATION**, all references to the Prodose® ADD® System were deleted.

3. Under **DESCRIPTION**, the following text was deleted from the first paragraph:

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

4. Under **PATIENT COUNSELING INFORMATION**, the following text was deleted from the first paragraph:

   > Patients receiving Ventavis should be advised to use the drug only as prescribed with ~~either of the two pulmonary drug delivery devices: the I-neb® AAD® System or the Prodose the~~ I-neb® AAD® System, following the manufacturer's instructions. 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.

5. Under **PATIENT COUNSELING INFORMATION/Preparation Instructions**, the following text was deleted from step #4:

   > After opening the ampule, use the small tube (pipette) supplied with Ventavis, draw-up the entire amount of one ampule of Ventavis and transfer the entire contents ~~of either the I-neb® AAD® System or the Prodose® AAD® System. If using the Prodose® AAD® System, two 10 mcg/mL ampules need to be added to the medication chamber~~ the ampule into the medication chamber of the I-neb® AAD® System.

The sponsor made the following changes to the PATIENT INFORMATION leaflet:

1. Under **What are the possible side effects of Ventavis?**, the following bullets were added/deleted:

   > ~~The most common~~Other important side effects of Ventavis include:
   > - bleeding
   > - red face (flushing)
   > - increased cough
   > - low blood pressure
   > - headaches
   > - nausea
   > - spasm of your jaw muscles that makes it hard to open your mouth
   > - ~~fainting~~

2. Under **Patient Instructions for Use**, all references to the Prodose ADD System were deleted.

3. The revision date and version number were updated.

There are no other changes from the last approved package insert.

We have completed our review of this supplemental 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, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of

labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.
Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

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:

Lori Anne Wachter, RN, BSN
Regulatory Project Manager for Safety
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

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

/s/

MARY R SOUTHWORTH
11/25/2013