DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21779/S-010 **SUPPLEMENT APPROVAL**

Actelion Pharmaceuticals, Ltd.
Attention: Mr. Brian Schlag, MA, MS
Associate Director, U.S. Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Mr. Schlag:

Please refer to your October 19, 2009, Supplemental New Drug Application (sNDA), received October 20, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ventavis (iloprost) 10 and 20 mcg/mL Inhalation Solution.

This "Prior Approval" supplemental new drug application provides for compliance with the Physician's Labeling Rule (PLR) including several revisions to the content of labeling as specified below.

1. In **DOSAGE AND ADMINISTRATION**, under **Recommended Dosing** (section 2.1), the following text was added to the first sentence in the second paragraph:

   …do not mix with other medications.

   Also, the preparation instructions for Ventavis were relocated from section 2.1 to section 17.1 under **PATIENT COUNSELING INFORMATION/Preparation Instructions**.

2. In **DOSAGE AND ADMINISTRATION, Monitoring** (section 2.2), the following text was deleted:

   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.

3. In **DOSAGE AND ADMINISTRATION**, **Use in patients with pre-existing hepatic impairment** (section 2.3), the following text was changed

   FROM

Because iloprost elimination is reduced in patients with impaired liver function, caution should be exercised during iloprost therapy in patients with at least Child Pugh Class B hepatic impairment.

TO

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

4. In **DOSAGE AND ADMINISTRATION**, **Use in patients with pre-existing renal impairment** (section 2.4), the following text was revised:

FROM

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.

TO

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

5. In **WARNINGS AND PRECAUTIONS**, several sections were revised as follows:

Beginning in section 5, the following text was deleted:

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. It has not been studied with any other nebulizers.

Direct mixing of Ventavis with other medications in the I-neb AAD System or the Prodose AAD System has not been evaluated.

In section 5.1, **Risk of Syncope**, the following text was modified

FROM

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.

TO

Monitor vital signs while initiating Ventavis. Do not initiate Ventavis in patients with systolic blood pressure below 85 mmHg. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

In section 5.2, **Pulmonary venous hypertension**, the following text was modified

FROM

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.

TO

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

In section 5.3, **Bronchospasm**, the following text was revised

FROM

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.

TO

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

6. In the beginning of section 6, **ADVERSE REACTIONS**, the following standard language was added:

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

7. Under section 6, **ADVERSE REACTIONS/Postmarketing Experience** (section 6.2), the following text was modified

   FROM

   Cases of dizziness and diarrhea have also been reported with the use of Ventavis.

   TO

   Cases of dizziness, diarrhea, mouth and tongue irritation, dysgeusia, hypersensitivity, and rash have also been reported with the use of Ventavis.

8. In the beginning of section 8, **Pregnancy**, the following sentence was added:

   Ventavis has been shown to be teratogenic in rats as described below.

9. In section 12.3, **Pharmacokinetics**/General, the term "serum" was replaced by "plasma" (second sentence of the second paragraph).

   Also, a sentence under **Pharmacokinetics**/Metabolism and Excretion was relocated from the third paragraph to the first paragraph within the same section.

10. In section 14, **CLINICAL STUDIES**, information regarding etiology of subjects in Table 1 and Table 2 was added as follows:

    Table 1
    ** etiologies of PAH, WHO Group I included idiopathic in 62% (n=90), associated with connective tissue disease, including CREST and scleroderma, in 17%, (n=25), associated with anorexigen use in 6% (n=9), familial PAH in 3% (n=5), other PPH in 3% (n=5), SLE in 1% (n=2), post-partum in 1% (n=2), and overlap/other in 5% (n=8).

    Table 2
    *Patients of all etiologies of PAH, including CTEPH.

11. Other minor labeling revisions were made to improve overall readability.

We have completed our review of this application, as amended. 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)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert, text for the patient package insert, and instructions for use). For administrative purposes, please designate this submission, "**SPL for approved NDA 21779/S-010**."

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, Pharm.D., 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
Content of Labeling

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21779	SUPPL-10	ACTELION PHARMACEUTICALS LTD	VENTAVIS (ILOPROST) INHALATION 10MCG/ML

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
04/20/2010