DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21290/S-019 **SUPPLEMENT APPROVAL**

Actelion Ltd.
Attention: Dr. Frances Duffy-Warren
VP Regulatory Affairs US
1820 Chapel Ave. West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Duffy-Warren:

Please refer to your supplemental New Drug Application (sNDA) dated December 17, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) Tablets.

This Prior Approval sNDA provides for the following revisions to the labeling for Tracleer (bosentan).

HIGHLIGHTS OF PRESCRIBING INFORMATION

1. In **INDICATIONS AND USAGE**, revise the following text

   FROM

   Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II to IV symptoms to improve exercise capacity and decrease clinical worsening (1.1).

   Considerations for use:
   Consider whether benefits offset the risk of liver injury in WHO Class II patients. Early liver injury may preclude future use as disease progresses (1.1).

   TO

   Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases

(21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%) (1.1).

Considerations for use:
Consider whether benefits offset the risk of liver injury in WHO Class II patients. Early liver injury may preclude future use as disease progresses (1.1).

Full Prescribing Information

2. In **INDICATIONS AND USAGE**, revise the following text

FROM

Tracleer® is indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II - IV symptoms, to improve exercise ability and decrease the rate of clinical worsening *[see Clinical Studies (14.1)]*.

Considerations for use
Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

TO

Tracleer® is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%) *[see Clinical Studies (14.1)]*.

Considerations for use
Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

Note that minor labeling revisions were made in section 14 of the labeling (**CLINICAL STUDIES**) to be consistent with the revisions made in section 1 (**INDICATIONS AND USAGE**).

We note that you also revised the manufacturer information from “Distributed by: Actelion Pharmaceuticals US, Inc.” to “Manufactured for: Actelion Pharmaceuticals US, Inc.”

We have completed our review of this supplemental application. 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, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert, Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. 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 pending "Changes Being Effected" (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.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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, MBA, BCPS, 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: Package Insert

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
02/08/2011