DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21290/S-022

SUPPLEMENT APPROVAL

Actelion Ltd.
Attention: Dr. Allen D. Nickol
Associate Director, Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Nickol:

Please refer to your Supplemental New Drug Application (sNDA) dated December 8, 2011, received December 8, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) 62.5 and 125 mg tablets.

We also acknowledge receipt of your amendments dated February 28, March 20, and July 2, 2012.

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

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

LABELING CHANGES

In the **HIGHLIGHTS** section of the package insert:

Revised text in **INDICATIONS AND USAGE**

FROM
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).

TO
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 heart disease with left-to-right shunts (18%) (1.1).

Deleted the following text in **WARNINGS AND PRECAUTIONS**

Use with caution in mild impairment.

In the **FULL PRESCRIBING INFORMATION** section of the package insert:

Revised text in **INDICATIONS AND USAGE**

FROM
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)]*.

TO
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 heart disease with left-to-right shunts (18%) *[see Clinical Studies (14.1)]*.

Revised text in **DOSAGE AND ADMINISTRATION/Use in Patients with Pre-existing Hepatic Impairment**

FROM
Tracleer should generally be avoided in patients with moderate or severe liver impairment. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function *[see Warnings and Precautions (5.2)]*.

TO
Tracleer should generally be avoided in patients with moderate or severe liver impairment. No dose adjustement is required in patients with mildly impaired liver function *[see Warnings and Precautions (5.2), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

Removed the ***[see BOXED WARNING]*** subheading in **CONTRAINDICATIONS**

Revised text in **WARNINGS AND PRECAUTIONS/Patients with Pre-existing Hepatic Impairment**

FROM
Tracleer is not recommended in patients with moderate or severe liver impairment. In addition, Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult *[see Boxed Warning, Dosage and Administration (2.5), Use in Specific Populations (8.6)]*.

TO
Tracleer is not recommended in patients with moderate or severe liver impairment. In addition, initiation of Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult *[see Boxed Warning, Dosage and Administration (2.5), Use in Specific Populations (8.6)]*.

Revised text in **USE IN SPECIFIC POPULATIONS**

FROM
Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated. There are no specific data to guide dosing in patients with mild hepatic impairment. Tracleer is not recommended in patients with moderate or severe liver impairment *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Pharmacokinetics (12.3)]*.

TO
Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. The pharmacokinetics of Tracleer has not been evaluated in patients with severe liver impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the systemic exposures to bosentan and its active metabolite increased significantly. Tracleer should generally be avoided in patients with moderate or severe liver impairment. Pharmacokinetics of bosentan was not altered in patients with mild impairment of hepatic function (Child-Pugh Class A) *[see Dosage and Administration (2.5), Warnings and Precautions (5.3), Pharmacokinetics (12.3)]*.

Revised text in **CLINICAL PHARMACOLOGY/Pharmacokinetics/Hepatic Impairment**

FROM

In vitro and *in vivo* evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. In a study comparing 8 patients with mild liver impairment (as indicated by the Child-Pugh method) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan was not altered in patients with mild hepatic impairment. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Use in Specific Populations (8.6)]*.

TO
In vitro and *in vivo* evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. In a study comparing 8 patients with mild liver impairment (Child-Pugh Class A) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan was not altered in patients with mild hepatic impairment.

In another small (N=8) pharmacokinetic study, the steady-state AUC of bosentan was on average 4.7 times higher and the active metabolite Ro 48-5033 was 12.4 times higher in 5 patients with moderately impaired liver function (Child-Pugh Class B) and pulmonary arterial hypertension associated with portal hypertension than in 3 patients with normal liver function and pulmonary arterial hypertension of other etiologies.

The pharmacokinetics of Tracleer has not been evaluated in patients with severe liver impairment (Child-Pugh Class C) *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), Use in Specific Populations (8.6)]*.

Revised text in **CLINICAL STUDIES**

FROM
Long-term Treatment of PAH
Long-term follow-up of patients with Class III and IV PAH who were treated with Tracleer in open-label extensions of trials (N=235) showed that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment. These uncontrolled observations do not allow comparison with a group not given Tracleer and cannot be used to determine the long-term effect of Tracleer on mortality.

Pulmonary Arterial Hypertension related to Congenital Systemic-to-Pulmonary Shunts
A small study with patients (N=54) with Eisenmenger physiology demonstrated effects of Tracleer on exercise and safety that were similar to those seen in other trials in patients with PAH (WHO Group 1).

TO
Long-term Treatment of PAH

Long-term follow-up of patients with Class III and IV PAH who were treated with Tracleer in open-label extensions of trials (N=235) showed that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment.

These uncontrolled observations do not allow comparison with a group not given Tracleer and cannot be used to determine the long-term effect of Tracleer on mortality.

Pulmonary Arterial Hypertension related to Congenital Heart Disease with Left-to-Right Shunts
A small study (n=54) and its open label extension (n=37) of up to 40 weeks with patients with Eisenmenger physiology demonstrated effects of bosentan on exercise and safety that were similar to those seen in other bosentan trials in patients with PAH (WHO Group 1).

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

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

Enclosures:

Package Insert
Medication Guide

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
10/04/2012