DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021290/S-025

SUPPLEMENT APPROVAL

Actelion Pharmaceuticals 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 and received December 7, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) 62.5 mg and 125 mg Tablets.

We also acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated January 18, 2012.

This supplemental new drug application provides for the use of Tracleer (bosentan) for the treatment of pulmonary arterial hypertension and proposed modifications to the approved risk evaluation and mitigation strategy (REMS).

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Tracleer (bosentan) was originally approved on August 7, 2009, and REMS modifications were approved on February 19, 2010 (and last modified on October 2, 2012). The REMS consists of a Medication Guide, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of changes to the Prescribers Essentials Guide, Dear Prescriber Letter, Prescriber Retraining Letter, Dear Hospital Letter, and REMS Website, and include:

The following text was revised in the Prescribers Essentials Guide, Dear Prescriber Letter, Prescriber Retraining Letter, and Dear Hospital Letter:

- "systemic-to-pulmonary" was replaced with "heart disease with left-to-right"

The following statement in the Prescribers Essentials Guide under Warnings and Precautions was moved from the 5th position to the 3rd position to match the order of the Warnings and Precautions:

- Pulmonary veno-occlusive disease (PVOD): If signs of pulmonary edema occur, consider the diagnosis of associated PVOD and consider discontinuing Tracleer (5.5).

In addition to the above changes, the following revisions were made to the REMS Website:

- Under Important Safety Information, Teratogenicity:

- [redacted] (b) (4) was revised to "Obtain monthly pregnancy tests."

- Under Warnings and Precautions:
  - [redacted] (b) (4) was revised to "Decreased sperm counts have been observed in patients receiving Tracleer. Preclinical data also suggest that Tracleer, like other endothelin receptor antagonists, may have an adverse effect on spermatogenesis."

- Under Warnings and Precautions:
  - [redacted] (b) (4) was revised (b) (4)

The timetable for submission of assessments of the REMS will remain the same as that approved on February 19, 2010.

There are no changes to the REMS assessment plan described in our October 2, 2012 letter.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA 021290 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 021290 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021290
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021290
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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, RAC
Regulatory Project Manager
(301) 796-3975

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD
Deputy Director for Safety
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

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
07/01/2013