DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21-290/S-018 **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 October 16, 2009, received October 20, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) Tablets.

We also refer to your submissions dated January 14, and February 2, 2010.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

This prior approval supplemental new drug application provides for modifications to the Tracleer (bosentan) Tablets REMS, originally approved on August 7, 2009. Modifications are proposed for the timetable for submission of assessments, as described below. Included in your submission is an assessment of the REMS comprised of a statement that the proposed modifications will not change the effectiveness of the REMS.

The proposed modification of the timetable for submission of assessments will harmonize with the reporting interval for other regulatory reports for Tracleer (bosentan) Tablets. The first reporting interval was from August 7, 2009 through November 19, 2009, and we received the report dated January 20, 2010. Each report thereafter will cover the yearly period November 20 through November 19, with the report to be submitted by January 19 each year.

Your proposed modified REMS, submitted on February 2, 2010, and appended to this letter, is approved. The proposed modified REMS contains the same Medication Guide, Elements to Assure Safe Use, and Implementation System as the original REMS, with the exception of the modifications to the timetable for submission of assessments listed above.

The REMS Assessment Plan will remain the same as that approved on August 7, 2009.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(A), an assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Assessments of an approved REMS also include, under section 505-1(g)(3)(B) and (C), information on the status of any post-approval study or clinical trial required under section 505(o) or otherwise undertaken to investigate a safety issue. You can satisfy these requirements in your REMS assessments by referring to relevant information included in the most recent annual report required under section 506B and 21 CFR 314.81(b)(2)(vii) and including any updates to the status information since the annual report was prepared. Failure to comply with the REMS assessments provisions in 505-1(g) could result in enforcement action.

We remind you that 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 FDCA.

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

NDA 021290 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 021290
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

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 also agree with your proposed change to the REMS supporting document concerning the manner of obtaining information about adverse events. Obtaining information about adverse events will now be the responsibility of Actelion Ltd. instead of the certified pharmacies, and you will treat all adverse events reported within the Tracleer (bosentan) Tablets REMS as solicited reports, instead of spontaneous reports. Therefore, the reports will not be submitted to FDA unless the adverse event meets the regulatory definitions of serious and unexpected and you have determined that there is a reasonable possibility that Tracleer (bosentan) Tablets caused the adverse experience. This change does not modify the current REMS requirement of expedited

handling of reports of pregnancy exposures and reports of liver injury, regardless of whether these reports are spontaneous or solicited.

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, RAC, Regulatory Project Manager, at (301)796-0578.

Sincerely,

{See appended electronic signature page}

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

Enclosure: Modified REMS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21290	SUPPL-18	ACTELION LTD	TRACLEER

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/s/

MARY R SOUTHWORTH
02/19/2010