



NDA 21-290/S-016

APPROVAL LETTER

Actelion Clinical Research, Inc.
Attn: Frances Duffy-Warren, PhD
VP US Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Dr. Duffy-Warren:

Please refer to your supplemental new drug application (sNDA) dated September 19, 2008, received September 22, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) 62.5 and 125 mg Tablets.

This amendment contained a proposed Risk Evaluation and Mitigation Strategy (REMS) and was submitted in accordance with section 909(b)(1) of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Under section 909(b)(1) of FDAAA, we identified Tracleer (bosentan) as a product deemed to have in effect an approved REMS because there were in effect on the effective date of FDAAA, March 25, 2008, elements to assure safe use required under 21 CFR 314.520.

We also refer to our correspondences dated February 18, and May 5, 2009, and your correspondence and submissions dated March 27 and July 31, 2009.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Tracleer (bosentan) to ensure the benefits of the drug outweigh the risks of hepatotoxicity and teratogenicity. Your proposed REMS, submitted on September 19, 2008, as amended, and appended to this letter, is approved. The REMS consists of the Medication Guide, elements to assure safe use, and the timetable for submission of assessments of the REMS and related documents appended to the REMS.

We acknowledge that you will continue to submit RiskMAP assessments for the period ending on August 7, 2009.

You will collect and report all data required for assessments of the approved REMS. The REMS Assessment Plan should include but is not limited to the following data:

1. Demographic data regarding patients enrolled in the Tracleer Access Program, including, by reporting period and overall:

- a. Total number of patients receiving Tracleer, stratified by age, gender and other demographics
 - b. The number of and person-years of exposure
 - c. Patient diagnosis
2. The number of and person-years of exposure for female patients of childbearing potential, by reporting period and overall
3. The number of patients with treatment interruptions, and the reasons for those treatment interruptions for the reporting period
4. Numbers, reasons, and lengths in days of shipment delays for the reporting period
5. Number of patients and reasons for dispensing > 30 day supply for the reporting period
 - a. An analysis of frequency of dispensing > 30 day supply by pharmacy
 - b. An analysis of prescribing > 30 day supply by prescriber and by unique patient (as identified by Actelion Control Number)
6. An analysis of the frequency of prescribing a daily dose > 250 mg per day, by prescriber and by patient for the reporting period
7. The number of times (percent) the patient reported to the pharmacy they had not completed laboratory testing for the reporting period
 - a. Monthly pregnancy testing for female patients of childbearing potential by quarter and overall
 - b. Liver function testing by quarter and overall
8. The number of times (percent) the patient reported an abnormal test result to the pharmacy for the reporting period
9. The number of times (percent) a shipment was held because the patient reported an abnormal test result to the pharmacy, and the length in days of the delayed shipment for the reporting period
10. The number and reasons for discontinuation for the reporting period and overall
11. An analysis of pregnancies,
 - a. pregnancy outcomes for exposed pregnancies, by reporting period and overall
 - b. the root-cause analysis of pregnancies in the reporting period to determine the reason the REMS failed to prevent the pregnancy exposure
 - c. The number of pregnancy exposures by reporting period and overall (pregnancy exposures will be recorded within the REMS database as well as

the global safety database, with appropriate linkage to allow matching of the cases reported in the REMS database to cases in the global safety database)

12. Summary of cases of liver injury, by reporting period and overall, including cases of serum transaminases $> 8 \times$ upper limit of normal (ULN); cases of serum transaminases $> 3 \times$ ULN accompanied by increases in serum bilirubin $\geq 2 \times$ ULN; and cases of liver injury associated with hospitalization, liver transplant, being listed for liver transplant or death
 - a. Analysis of cases of liver injury in the reporting period
13. Summary data on certified prescribers, for the reporting period and overall, including:
 - a. Number of certified prescribers
 - b. Stratification based on specialty
14. Data and analysis on certified pharmacies, for the reporting period, including but not limited to:
 - a. Distribution data from the certified pharmacies
 - b. Compliance with liver function and pregnancy testing monitoring data
 - c. Distribution and dispensing of the Medication Guide in accordance with 21 CFR§ 208.24
 - d. Reports of operational audits, including results of distribution data reconciliation
 - e. A Pharmacy Compliance Report including the need for intervention with each certified pharmacy and corrective actions taken to address noncompliance
15. Survey data obtained during the reporting period assessing patient and prescriber understanding of risks of Tracleer
16. An analysis of complaints spontaneously obtained during the reporting period received from patients about the burden of the REMS
17. With respect to REMS goals, an assessment of the extent to which the elements to assure safe use are meeting the goals or whether the goals or such elements should be modified

The requirements for assessments of an approved REMS under section 505-1(g)(3) include, in section 505-1(g)(3)(B) and (C), requirements for information on the status of any postapproval 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 amendment 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 21-290 REMS ASSESSMENT

**NEW SUPPLEMENT FOR NDA 21-290
PROPOSED REMS MODIFICATION
REMS ASSESSMENT**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 21-290
REMS ASSESSMENT**

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

DEAR HEALTHCARE PROFESSIONAL LETTER

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, “**SPL for approved NDA 21-290/S-016**” or alternatively “**SPL for approved NDA 21-290/S-012.**” We request that the revised 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, 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: REMS

Medication Guide

Final product labeling

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
08/07/2009