



NDA 021290/S-032  
NDA 209279/S-004

**SUPPLEMENT APPROVAL**

Actelion Pharmaceuticals, Ltd.  
c/o: Actelion Clinical Research, Inc.  
Attention: Lori A. Palmer  
Director, US Regulatory Affairs  
1820 Chapel Avenue West, Suite 300  
Cherry Hill, NJ 08002

Dear Ms. Palmer:

Please refer to your Supplemental New Drug Application (sNDA) dated and received July 28, 2016 (NDA 021290) and October 16, 2018 (NDA 209279), and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) tablets, 62.5 mg and 125 mg (NDA 021290) and Tracleer (bosentan) tablets for oral suspension, 32 mg (NDA 209279).

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Tracleer risk evaluation and mitigation strategy (REMS) and analogous changes to the approved Tracleer labeling.

**APPROVAL & LABELING**

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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as 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 that include labeling changes 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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.

### **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

The REMS for Tracleer was originally approved on August 7, 2009, and the most recent REMS modification was approved on October 20, 2017. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS establish a Single Shared System REMS for the elements to assure safe use and the implementation system required for the reference listed drug (RLD) Tracleer and ANDAs referencing Tracleer, called the Bosentan REMS Program. This modification also removes the Medication Guide as an element of the REMS.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS:

**REMS Goals:** The overall goals of the Bosentan REMS remain the same; however, the presentation of the REMS goals was updated to better articulate how the REMS is structured to mitigate the risks.

**Medication Guide:** We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in 21 CFR 208. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Tracleer outweigh its risks. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208. Like other labeling, Medication

Guides are subject to the safety labeling change provisions of section 505(o)(4) of the FDCA.

Your proposed modified REMS, initially submitted on July 28, 2016, for NDA 021290/S-032 and on October 16, 2018, for NDA 209279/S-004, amended and appended to this letter, is approved. The modified REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS must be revised to one year from the date of the initial approval of Single Shared System REMS (04/26/2019) and annually thereafter.

The revised REMS assessment plan must include, but is not limited to, the following:

**1. Program Implementation (for the 12-month assessment only)**

- a. Bosentan REMS Program Launch Date
- b. Date when Bosentan REMS Program materials became available on the website and via the Contact Center
- c. The dates stakeholders could enroll online, by mail, by fax:
  - i. Prescribers
  - ii. Pharmacies
  - iii. Patients
- d. Date when the *Bosentan REMS Program Website* went live
- e. *Bosentan REMS Program Website* utilization
  - i. Number of unique visitors
  - ii. Number of visits
  - iii. Average number of page views per visit
  - iv. Total page views

**2. REMS Program Utilization (for each reporting period and cumulatively)**

- a. Prescribers
  - i. Number of certified prescribers, and the number and percentage of enrolled health care providers who have prescribed Bosentan stratified by medical specialty
- b. Pharmacies
  - i. Number of certified pharmacies by pharmacy type (inpatient, outpatient, and chain)
  - ii. Number of deactivated pharmacies, and a summary of reasons for deactivation
- c. Patients
  - i. Number and percentage of enrolled patients by patient type:
    - 1) Males
    - 2) Females of reproductive potential (FRP)
    - 3) Pre-pubertal females (as classified on the ***Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form***)
    - 4) Females of non-reproductive potential (FNRP)
  - ii. Number of patients, new and total, by patient type grouped by the following age ranges
    - 1) < 6
    - 2) 6 - < 18
    - 3) 18 - < 65
    - 4) 65+

**3. Reproductive Potential Status Changes (for each reporting period and cumulatively)**

Both in a flowchart and in the report narrative, report the following regarding the *Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Forms* including:

- a. Number of forms received, including the number of forms received in error and the reasons these are classified as errors
- b. Number of status changes to an FRP, including the rationale for the change as indicated on the form. Also report:
  - 1) Time between receipt of form and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)
  - 2) Verification that routine monthly pregnancy tests of all FRPs occurred prior to the next dispense following the prescriber becoming aware of a change in status to an FRP
  - 3) Number of times Bosentan was dispensed prior to the patient getting their first pregnancy test following the prescriber becoming aware of the status change to FRP, any resulting adverse events, and corrective action
- c. Number of status changes to an FNRP, including rationale for the change as indicated on the form
- d. The number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female
- e. The number of Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Forms returned reporting annual verification that a patient remains a Pre-Pubertal Female that are expected
- f. Number of instances where a prescriber did not report a change or misclassification in the reproductive status of any female patient within 10 business days of becoming aware of the change

- g. Conduct a root cause analysis of all cases of reproductive status misclassifications and include the protocol used to conduct this root cause analysis

**4. Contact Center Report (for each reporting period and cumulatively)**

For the current reporting period, provide:

- a. Number of Contacts by reporter type (e.g., pharmacy, prescriber, patient)
- b. Summary of reason for call (e.g., “Enrollment question”, etc.) by reporter (e.g., pharmacy, prescriber, patient)
- c. Narrative of any corrective actions resulting from issues identified

**5. Pharmacy and Distributer Audit Summary (for each reporting period and cumulatively)**

- a. Provide a report of audit activities for certified inpatient and outpatient pharmacies and distributors performed during the reporting period to include:
  - i. The number of audited sites in each category (i.e. certified outpatient pharmacies, certified inpatient pharmacies, and certified wholesalers/distributors)
  - ii. A summary of critical observations identified during audits and corrective actions taken to address any noncompliance including but not limited to whether any required corrective and preventive action (CAPA) plans were initiated and satisfactorily completed during the reporting period. A comparison of the findings to findings of previous audits and assess whether any trends are observed
  - iii. An overview of the annual audit plan

**6. Bosentan REMS Program Compliance (for each reporting period and cumulatively)**

- a. Number of bosentan prescriptions dispensed that were written by non-certified or deactivated prescribers, actions taken to prevent future occurrences, and the outcome of such actions

- b. Number of prescriptions dispensed by noncertified pharmacies, actions taken to prevent future occurrences, and outcome of such actions
- c. Number of shipments sent to noncertified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions
- d. The number of certified prescribers and/or pharmacies that have had their certification suspended or deactivated, including the reasons for such action
- e. An evaluation of dispensing delays which resulted in an actual treatment interruption (defined as a delay in treatment of one or more days) due either to the absence of liver and/or pregnancy test results, or due to pharmacy and/or prescriber error:
  - i. The mean and median duration (including the standard deviation) of the observed treatment interruptions
  - ii. A root cause analysis to identify why either the pregnancy and/or liver testing wasn't completed or source of the pharmacy and/or prescriber error
  - iii. Any adverse events resulting from the treatment interruption
- d. Number of prescriptions dispensed of greater than 30-day supply
- e. Noncompliance with the Bosentan REMS Program requirements, source of report(s), and any corrective action(s) or resolution(s)

**7. REMS Infrastructure Performance (for each reporting period and cumulatively)**

- a. False negatives: i.e., all REMS and safe use requirements were met, but a pre-dispense authorization was not provided by the Bosentan REMS Program, and corrective actions taken
- b. False positives: i.e., all REMS and safe use requirements were not met, but a pre-dispense authorization was provided by the Bosentan REMS Program, and summary of corrective actions taken
- c. Inadvertent stakeholder deactivations and corrective actions taken
- d. Unintended system interruptions and corrective actions taken

- e. Other barriers or delays in product dispensation and corrective actions taken
  - f. PDAs provided on first pharmacy attempt (i.e., Number of pre-dispense authorizations that did not encounter any rejections prior to being authorized)
  - g. Total number of authorizations that encountered one or more pre-dispense authorization rejections; provide the reasons for such rejections
- 8. Evaluation of Knowledge of the Bosentan REMS Program and Risks of Bosentan/Surveys (For the 12-month and all subsequent REMS assessments submitted annually)**
- a. An evaluation of certified prescriber's knowledge of: the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan, the need to monitor patients at baseline and monthly, the need to counsel patients about the risks and monitoring, and the need to enroll patients in the Bosentan REMS program
  - b. An evaluation of pharmacy authorized representatives' and trained pharmacists' knowledge of the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan and the need to confirm that appropriate patient monitoring and counseling occur before dispensing bosentan
  - c. An evaluation of patients' knowledge of the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan, appropriate baseline and monthly monitoring, and appropriate contraception
- 9.** 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 one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

- a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
- b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
- c) *If the new indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
- d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.
- e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
- f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including:* Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications, provide a rationale for why the REMS does not need to be modified.*

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 021290, NDA 209279 REMS 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.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any 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, NDA 209279 REMS ASSESSMENT**

*or*

**NEW SUPPLEMENT FOR NDA 021290/S-000, NDA 209279/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 021290/S-000, NDA 209279/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR NDA 021290/S-000, NDA 209279/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES  
SUBMITTED IN SUPPLEMENT XXX**

*or*

**NEW SUPPLEMENT (NEW INDICATION FOR USE)  
FOR NDA 021290/S-000, NDA 209279/S-000  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

**REMS REVISIONS FOR 021290, NDA 209279**

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such

as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

### **SUBMISSION OF REMS DOCUMENT IN SPL FORMAT**

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

### **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 for Safety  
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:  
CONTENT OF LABELING  
REMS

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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MARY R SOUTHWORTH  
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