



NDA 209279

NDA APPROVAL

Actelion Pharmaceuticals, Ltd.
Attention: Lori Palmer
Director, US Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Ms. Palmer:

Please refer to your New Drug Application (NDA) dated and received August 5, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) 32 mg Dispersible Tablets.

We acknowledge receipt of your major amendment dated April 4, 2017, which extended the goal date by three months.

We also refer to your Approval letter dated September 5, 2017. The September 5, 2017 Approval letter contains an error: The REMS document was not attached to the letter. This letter supersedes and corrects the error in the September 5, 2017 letter. The approval date will remain September 5, 2017.

This new drug application provides for the use of Tracleer[®] (bosentan) Dispersible Tablets for the treatment of Pulmonary Arterial Hypertension in adult and pediatric patients.

We have completed our review of this application, as amended. 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 package insert, Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible via publicly available labeling repositories. We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 209279.**” Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

- 3265-1 Develop and submit Chemistry, Manufacturing and Controls information supporting a change to the scoring of the tablet, i.e. changing the tablet from quadrisectioned to bisected.

The timetable you submitted on August 14, 2017 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 04/2018
Final Report Submission: 11/2019

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Tracleer (bosentan) Dispersible Tablets to ensure the benefits of the drug outweigh the risks of hepatotoxicity and teratogenicity.

Your proposed REMS must include the following:

Medication Guide: In accordance with section 505-1 of FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that Tracleer (bosentan) Dispersible Tablets pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Tracleer (bosentan) Dispersible Tablets. FDA has determined that Tracleer (bosentan) Dispersible Tablets is a product for which patient labeling could help prevent serious adverse effects and that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Tracleer (bosentan) Dispersible Tablets. Under section 505-1 of the FDCA, FDA has also determined that a Medication Guide is necessary to ensure the benefits of the drug outweigh the risks of hepatotoxicity and teratogenicity.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Tracleer (bosentan) Dispersible Tablets.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Tracleer (bosentan) Dispersible Tablets can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of hepatotoxicity and teratogenicity listed in the labeling. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. The elements to assure safe use will ensure patients receive ongoing liver enzyme and pregnancy monitoring prior to and during Tracleer (bosentan) Dispersible Tablets therapy.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and

the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS, submitted on August 25, 2017 and appended to this letter, is approved. 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.

Tracleer Dispersible Tablets will be subject to the same REMS as Tracleer (bosentan) Tablets (NDA 21290), known as the Tracleer REMS. Consequently, Tracleer Dispersible Tablets will be subject to the same assessment plan in the Tracleer REMS, and align with the subsequent assessments of the Tracleer REMS.

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

- a. Enrollment into the Tracleer REMS Program:
 - Patients: new and total, age, gender
 - Prescribers: new and total, specialty
 - Pharmacies: new and total
 - Hospitals: new and total
 - Distributors: new and total
- b. Pregnancies
 - Number of new pregnancy reports
 - Outcome of each new pregnancy report
 - Follow-up of outstanding pregnancy reports from previous assessment reporting period
 - Root cause analysis of each newly reported pregnancy
 - Link to most recent PSUR report on pregnancies worldwide; discussion of any new information provided in the PSUR regarding pregnancy
 - Overall summary of all cases particularly addressing whether any cases consistent with human teratogenicity have been identified
- c. Summary of serious hepatic events as reflected in the periodic liver safety update (LSUR) reports: provide a comparison of most recent analysis of these events to previous analyses with emphasis on whether the safety profile has changed. Include a link to the most recent LSUR
- d. Certified Pharmacy compliance with the REMS
 - Distribution data from the certified pharmacies
 - Compliance with liver and pregnancy testing monitoring data
 - Reports of operational audits, including results of distribution data reconciliation
 - Pharmacy Compliance Report including the need for intervention with each certified pharmacy and corrective actions taken to address noncompliance

- e. Distribution and dispensing of the Medication Guide in accordance with 21 CFR§ 208.24
- f. 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

Provide information to address each requirement for the current reporting period and for previous reporting periods. When possible, a tabular format is recommended.

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.

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 of 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). 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, proposed 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 the 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 a REMS modification, 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 209279 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.

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 209279 REMS ASSESSMENT

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

or

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

or

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

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR 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 REVISION FOR 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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 REMS_Website@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

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 Maryam Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Product
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure(s):

Content of Labeling
Carton and Container 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/

NORMAN L STOCKBRIDGE
09/05/2017