NDA 021290/S-048
NDA 209279/S-015

SUPPLEMENT APPROVAL

Actelion Pharmaceuticals US, Inc.
c/o Janssen Research and Development (US Agent)
Attention: Michelle Godin
Associate Director, Clinical Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Michelle Godin:

Please refer to your supplemental new drug applications (sNDAs) dated and received May 9, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) tablets for oral use (NDA 021290) and Tracleer (bosentan) tablets for oral suspension (NDA 209279).

These Prior Approval sNDAs provide for proposed modifications to the approved Bosentan Risk Evaluation and Mitigation Strategy (REMS) to release the REMS for embryo-fetal toxicity and changes to the approved labeling to remove all references to the REMS for embryo-fetal toxicity. This supplement is in response to our March 11, 2025, REMS Modification Notification letter.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 FDA.gov.[1] 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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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*.[2]

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 Shared System (SS) REMS for bosentan products, of which Tracleer is a member, was originally approved on April 26, 2019, and the most recent REMS modification was approved on February 21, 2025. The SS REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

In order to ensure the benefits of bosentan outweigh its risks of embryo-fetal toxicity and to minimize burden on the healthcare delivery system of complying with the REMS, we determined that you were required to make the REMS modifications outlined in our REMS Modification Notification letter dated March 11, 2025.

Elements to Assure Safe Use: We have determined that elements to assure safe use for the risk of embryo-fetal toxicity are no longer necessary based on an evaluation of human fetal outcomes reported from 2001 to 2024 after exposure to a drug in the endothelin receptor antagonist (ERA) pharmacologic class. These data have not shown a pattern of congenital malformations consistent with what was observed in animal embryo-fetal toxicity studies that supported the need for a REMS. Given the re-evaluation of the extent of the clinical risk based on animal findings, we have determined that labeling is sufficient for conveying information about the embryo-fetal risk and its mitigation. ETASU required to mitigate the risk of hepatotoxicity are not impacted by this change.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Implementation System: In addition, because the elements to assure safe use related to the risk of embryo-fetal toxicity requiring that pharmacies, practitioners, or health care settings that dispense the drug be specially certified and that the drug be dispensed to patients with documentation of safe use conditions are no longer necessary, the implementation system for the elements to assure safe use related to the risk of embryofetal toxicity is also no longer necessary as an element of the REMS. Aspects of the implementation system for the ETASU required to mitigate the risk of hepatotoxicity are not impacted by this change.

Your proposed modified REMS, submitted to Drug Master File (DMF) 035286 on May 8, 2025, amended and appended to this letter, is approved. The modified REMS for hepatotoxicity consists of elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

This shared system REMS, known as the Bosentan REMS, currently includes products listed on the FDA REMS website[3].

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on April 26, 2019.

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

For each metric, provide the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted.

Implementation and Operations

1. **REMS Certification and Enrollment Statistics**

    a. Prescribers
        i. Number and percentage of newly certified prescribers, and the number and percentage of active prescribers (i.e., who have prescribed bosentan, regardless of when they became certified) stratified by professional designation (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant), by medical specialty (e.g., Cardiology, Pulmonology, Rheumatology, General/Family Practice, Other), and geographic region (as defined by US Census)

[3] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

ii. Method of prescriber certification (online or via the Contact Center)

b. Prescriber Designees

i. Number and percentage of newly enrolled prescriber designees

ii. Number and percentage of active prescriber designees (associated with an active prescriber, regardless of when they were enrolled)

c. Pharmacies

i. Number and percentage of newly certified pharmacies and the number and percentage of active certified pharmacies (stratified by pharmacy type (i.e., chain, outpatient, inpatient, regardless of when they became certified), and geographic region (as defined by US Census). For outpatient pharmacies, active is defined as those pharmacies that have generated a Pre-Dispense Authorization PDA during the reporting period; starting with the Year 5 Assessment Report, for inpatient pharmacies, active is defined as those inpatient pharmacies that have ordered bosentan during the reporting period.

ii. Method of pharmacy certification (online or via the Contact Center)

d. Patients

i. Number and percentage of newly enrolled patients and the number and percentage of active patients (i.e., have received an approved PDA or had an inpatient REMS Requirement Verification, regardless of when they became enrolled) stratified by geographic region (defined by US Census)

ii. Number and percentage of patients who have discontinued therapy and the reason for discontinuation

iii. Method of patient enrollment (online or via the Contact Center)

e. Wholesalers-Distributors

i. Number and percentage of wholesalers-distributors newly enrolled

2. **Bosentan Utilization Data**

    a. Number and percentage of unique patients who received bosentan, stratified by newly enrolled and total number of enrolled patients

    b. Number and percentage of prescriptions (first fills and refills), dispensed by outpatient pharmacies, and stratified by prescriber specialty

    c. Include a description of the data source(s) used to obtain actual dispensing information (i.e., number of unique patients and the number of dispenses), including any known limitations of the utilization data source(s) and any methods used to address these limitations

3. **REMS Contact Center**

    a. Number of contacts by participant type (e.g., pharmacy, prescriber, prescriber designee, patient, wholesaler-distributor, other)

    b. Summary of reason for call (e.g., “Enrollment question,” location of a pharmacy, etc.) by participant type (e.g., pharmacy, prescriber, prescriber designee, patient, wholesaler-distributor, other)

    c. Summary of REMS-related problems identified and narrative of any resulting corrective actions

4. **REMS Website**

    a. Number of visits and unique visits to the **REMS Website**

    b. Number of REMS materials downloaded for each material

    c. Number of PDAs obtained through the **REMS Website** stratified by participant type that entered testing and patient counseling information through the **REMS Website** (e.g., certified pharmacies, prescribers, or prescriber designees)

5. **Audit Summary**

    a. Provide a report of audit findings for each participant type (i.e., inpatient pharmacies, outpatient pharmacies, enrolled wholesalers-distributors, and the REMS Contact Center) including but not limited to:

i. A summary of the annual audit plan for each participant type

ii. The number of audits expected per the REMS Document and the number of audits completed for each participant type listed directly above. If the number of expected audits is less than the number completed, provide an explanation of why and any corrective actions taken.

iii. The number and type of deficiencies noted for each group of audited participants

iv. For those with deficiencies noted, report the number that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan

1) A summary of critical, major, and minor 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

v. For any that did not complete the CAPA within the timeframe specified in the audit plan, describe the actions taken

vi. Use a unique ID for participants that had deviations to track deviations by participants over time

vii. Confirm documentation of completion of training for relevant staff

viii. Verify the existence of documented processes and procedures for complying with the REMS

ix. A comparison of the findings to findings of previous audits and assess whether any trends are observed

6. **REMS Compliance**

a. Provide a summary of noncompliance identified, including but not limited to:

i. A copy of the Noncompliance Plan which addresses the criteria for

noncompliance for each participant, actions taken to address noncompliance for each event under what circumstances a participant would be suspected or decertified from the REMS

b. The number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

   i. The unique ID(s) of the participant(s) associated with the noncompliance event or deviation to enable tracking over time

   ii. The source of the noncompliance data

   iii. The results of root cause analysis

   iv. What action(s) were taken in response and whether any follow-up is planned

c. Number of bosentan prescriptions dispensed that were written by noncertified or deactivated prescribers, source of report(s), actions taken to prevent future occurrences, and the outcome of such actions

d. Number of prescriptions dispensed by noncertified pharmacies, actions taken to prevent future occurrences, and outcome of such actions

e. Number of shipments sent to noncertified pharmacies, source of report(s), actions taken to prevent future occurrences, and outcome of such actions

f. The number of certified prescribers and/or pharmacies that have had their certification suspended or deactivated, including the reasons for such action

g. Number and percentage of pharmacies by type (i.e., inpatient and outpatient, which includes pharmacies classified as chain and outpatient) that did not provide verification of the Authorized Representative name and contact information every two years

h. 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 test results, or due to pharmacy and/or prescriber error. For each treatment interruption, include:

i. The mean and median duration (including the standard deviation) of the observed treatment interruptions

ii. A root cause analysis to identify why the liver testing wasn't completed or source of the pharmacy and/or prescriber error along with the protocol used to conduct the root cause analysis

iii. Any adverse events resulting from the treatment interruption

i. Number of total refill dispense exceptions (RDEs) authorized

i. Of the total number of RDEs authorized,

1) Number authorized when testing was not completed/confirmed (i.e., the prescriber used clinical judgement and allowed the RDE)

2) Number authorized for extended travel outside the U.S. (i.e., travel greater than 30 days)

j. Number of prescriptions dispensed of greater than 30 days' supply and a breakdown of reasons for dispensing (i.e., prescriber authorizations, prescriber noncompliance, other). Include any corrective actions as appropriate

k. False negatives (i.e., all REMS and safe use requirements were met, but a PDA was not provided by the Bosentan REMS, and corrective actions taken)

l. False positives (i.e., all REMS and safe use requirements were not met, but a PDA was provided by the Bosentan REMS, and summary of corrective actions taken)

m. Inadvertent participant deactivations and corrective actions taken

n. Unintended system interruptions and corrective actions taken

o. Other barriers or delays in product dispensation and corrective actions taken

Safe Use Behaviors

7. **Report on PDAs**

   a. Comparison of PDAs generated versus prescriptions for bosentan dispensed by outpatient pharmacies during the reporting period including:

      i. Total number of PDAs generated after deduplication, if possible, to ensure each unique PDA is counted once.

      ii. The proportion of deduplicated PDAs generated, out of the total number of deduplicated PDAs generated plus number of confirmed reported dispenses without a PDA, expressed as a percent

      iii. For the calculated proportion, indicate all data sources, processing steps, and validation methods applied to the data feeds into the calculation. Provide an assessment of data quality, including completeness rates, accuracy validation, and any known limitations or reliability concerns

   b. Number of prescriptions dispensed without a PDA, including:

      i. The unique ID(s) of the participant(s) associated with the noncompliance event or deviation to enable tracking over time

      ii. The source of the noncompliance data

      iii. The results of root cause analysis

      iv. What action(s) were taken in response and whether any follow-up is planned

   c. PDAs provided on first pharmacy attempt (i.e., Number of PDAs that did not encounter any rejections prior to being authorized) and stratified by participant type who entered testing and patient counseling information through the **REMS Website** (e.g., certified pharmacy staff, prescriber designees, REMS Contact Center staff, prescribers)

   d. Total number of authorizations that encountered one or more PDA rejections; provide the reasons for such rejections and stratified by participant type who entered testing and patient counseling information

through the **REMS Website** (e.g., certified pharmacy staff, prescriber designees, REMS Contact Center staff, prescribers)

Health Outcomes and/or Surrogates of Health Outcomes

8. **Hepatic Adverse Events**

   Each manufacturer will provide an analysis of all cases of a serious hepatic events reported in association with bosentan from any source including but not limited to the following:

   a. The criteria used to determine that the event is a serious hepatic event

   b. The number of new serious hepatic events

   c. The rate of serious hepatic events. Include incidence rates (in-person years) for serious hepatic events to allow comparison with expected rates in the general population.

   d. The case report number, as well other descriptive case information such as the patient's age, gender, and duration of bosentan therapy

   e. Outcome of each new serious hepatic event

   f. A comparison of most recent analysis of these events to previous analyses with emphasis on whether the safety profile has changed

   g. Follow-up of outstanding serious hepatic event reports from previous assessment reporting period

Overall Assessment of REMS

9. The requirements for assessments of an approved REMS under section 505-1(g)(3) of the FDCA 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
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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/NDA 209279
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021290/NDA 209279
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 021290/NDA 209279 PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 021290/NDA 209279
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 NDA 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

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

ENHANCED PHARMACOVIGILANCE

We request that you provide a summary analysis of reports of pregnancy and embryo-fetal and neonatal toxicity as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], for 3 years following approval of the REMS Modification.

Your analysis should include interval and cumulative data from clinical trials, postmarketing reports, and published literature relative to the date of the approval of the REMS modification. Your analysis should include at a minimum the cumulative number of reported pregnancies, pregnancy outcome [such as live birth, stillbirth, miscarriage, elective termination, congenital anomaly and type], and an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, and underlying risk factors.

If you have any questions, contact Lori Anne Wachter, RN, BSN, RAC – Drugs (US), Regulatory Health Project Manager for Safety, at 301 796-3975 or lori.wachter@fda.hhs.gov.

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Sincerely,

{See appended electronic signature page}

Selena DeConti, PharmD, MPH
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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.

/s/

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