NDA 021290/S-043
NDA 209279/S-009

SUPPLEMENT APPROVAL

Actelion Pharmaceuticals US, Inc.
Attention: Tamara Mazza, PhD.
Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Dr. Mazza:

Please refer to your supplemental new drug application (sNDA) dated and received November 4, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tracleer (bosentan) Tablets (NDA 021290) and Tracleer (bosentan) Tablets for Oral Suspension (NDA 209279).

This Prior Approval supplemental new drug application provides for proposed modifications to the approved Bosentan risk evaluation and mitigation strategy (REMS). We have completed our review of this supplemental application, as amended. It is approved effective on the date 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. The SS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of:

1. Changes to the outpatient pharmacy operations to verify safe use conditions for the REMS Pre-Dispense Authorization (PDA).
2. Addition of the Prescriber Designee role on the REMS website to allow prescribers to delegate certain administrative activities.
3. Changes to the REMS website to allow certified pharmacies to enter testing and counseling information through the REMS website and allow pharmacists requesting a PDA to confirm counsling information.
4. Changes to the pre-recorded messages in the Interactive Voice Response (IVR) system to align with the proposed modifications and new workflow.
5. Conversion of the REMS Document to the new, standardized format.

Your proposed modified REMS, submitted to Drug Master File (DMF) 035286 on November 11, 2021, amended and appended to this letter, is approved.

The modification of the approved REMS must be fully implemented within 60 calendar days of this letter.

This shared system REMS, known as the Bosentan REMS Program, currently includes products listed on the FDA REMS website[1].

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:

Program Implementation and Operations

1. **Bosentan REMS Program Website utilization (first assessment post-modification approval only)**
    a. Number of unique visitors
    b. Number of visits
2. **REMS Contact Center (first assessment post-modification approval only) the following:**
    a. Number and percentage of calls received (inbound) and of calls made (outbound)
    b. The average hold times (hours) for calls received (inbound) by the REMS Contact Center
    c. The average handle time (minutes) for calls received (inbound) by the REMS Contact Center
    d. Number of calls abandoned and the average wait to abandon (hours) for calls received (inbound) by the REMS Contact Center
    e. The percentage of queue wait times (i.e. less than 1 hour, 1 – 3 hours, 3 – 5 hours, and 5 – 8 hours) for calls received (inbound) by the REMS Contact Center
    f. The shortest queue wait time (hours) and longest queue wait time (hours)

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

g. Number of calls received that reached a high call volume message

h. Number of unique phone numbers

3. Stakeholder Transition (first assessment post-modification approval only)

a. For each stakeholder category (healthcare providers, prescriber designees, pharmacies, patients, and wholesalers/distributors) report:

i. Number transitioned into the modified Bosentan REMS

ii. Number certified or enrolled or registered in the REMS program prior to implementation of the modified Bosentan REMS

4. REMS Certification and Enrollment Statistics (provide previous, current, and cumulative reporting periods)

a. Healthcare Providers

i. Number and percentage of newly certified healthcare providers, and the number and percentage of active healthcare providers (i.e. who have prescribed bosentan) 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)

ii. Method of healthcare provider certification (online, fax or mail)

b. Prescriber Designees

i. Number and percentage of newly registered prescriber designees

ii. Number and percentage of active prescriber designees (associated with active prescriber)

c. Pharmacies

i. Number and percentage of newly certified pharmacies and the number and percentage of active certified pharmaciesstratified by pharmacy type (i.e. chain, inpatient, outpatient) and geographic region (as defined by US Census). For outpatient pharmacies, active is defined as those pharmacies that have generated a pre-dispensing authorization (PDA) during the current reporting period; for inpatient pharmacies, active is defined as those inpatient pharmacies that have ordered bosentan during the current reporting period.

ii. Method of pharmacy certification (online, fax or mail)

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 verification for bosentan) stratified by geographic region (defined by US Census) and 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)

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

ii. Method of patient enrollment (online, fax or mail)

e. Wholesaler/Distributors

i. Number and percentage of wholesaler/distributors newly authorized to distribute

5. Bosentan Utilization Data (provide previous, current, and cumulative reporting periods)

a. Number and percentage of unique patients who

received bosentan, new and total, by patient type grouped by the following age ranges

i. <10
ii. 10 - < 18
iii. 18 - < 25
iv. 25 - <45
v. 45 - <53
vi. 53+

b. Number and percentage of outpatient by pharmacy type (i.e. chain, outpatient) prescriptions (first-fills and refills) dispensed for each patient population type (male, FRPs, and FNRPs) stratified by:
   i. Healthcare Provider Specialty
   ii. Reproductive Status (FRP or FNRP)
   iii. Patient age as outlined in 2a above

6. REMS Contact Center (provide previous, current, and cumulative reporting periods)

a. Number of contacts by stakeholder type (e.g., pharmacy, healthcare provider, prescriber designee, patient, wholesaler(s)/distributor(s), other).

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

c. The average hold times for calls received by the REMS Contact Center

d. Summary report of REMS related problems identified and narrative of any resulting corrective actions.

7. 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 stakeholder type that entered testing and counseling information through the REMS website (e.g. certified pharmacies, prescriber designee or healthcare providers)

Safe Use Behaviors

8. **Report on Change in Reproductive Potential Status Changes and Pre-pubertal Annual Verification Form Data (provide previous, current, and cumulative reporting periods)**

   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:
      i. Time between receipt of form and confirmation that monthly pregnancy testing occurred (time reported as a mean, median and standard deviation)
      ii. Verification that routine monthly pregnancy tests of all FRPs occurred prior to the next dispense following a change in status to an FRP
      iii. Number of times Bosentan was dispensed prior to the patient getting their first pregnancy test following 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
      i. For any forms expected for a Pre-Pubertal female, but not received, conduct follow-up in order to determine the cause, outcome and any corrective actions taken

   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.

9. Audit Summary (provide previous, current and cumulative~~ly~~ reporting periods)

a. Provide a report of audit findings for each stakeholder (e.g. certified inpatient and outpatient (i.e. chain, outpatient) pharmacies, enrolled wholesalers/distributors, and the REMS Contact Center) including but not limited to:

i. A copy of the annual audit plan for each stakeholder

ii. The number of audits expected, and the number of audits conducted in each category listed directly above

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

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 actions taken

vi. Use a unique ID for stakeholders that had deviations to track deviations by stakeholders 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, if applicable

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

10. REMS Compliance (provide previous, current and

cumulative reporting periods)

a. Provide a summary of non-compliance identified, including but not limited to:
   i. A copy of the Non-Compliance Plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or de-certified 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 stakeholder(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 non-certified 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 prescriptions dispensed without a pre-dispensing authorization (PDA)

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

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

h.

i. Number and percentage of pharmacies by type (i.e. inpatient, outpatient (i.e. chain,outpatient) that did not provide verification of the authorized representative every two years.

j. 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. Include the mean and median duration (including the standard deviation) of the observed treatment interruptions. For each treatment interruption, include:

i. 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 along with the protocol used to conduct the root cause analysis.

ii. Any adverse events resulting from the treatment interruption

k. 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. 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).

l. Number of prescriptions dispensed of greater than 30-day supply and a breakdown of reasons for the dispensings (i.e. prescriber authorization, prescriber non-compliance, other). Include any corrective actions as appropriate.

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

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

o. Inadvertent stakeholder deactivations and corrective actions taken

p. Unintended system interruptions and corrective actions taken

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

Safe Use Behaviors

11. Report on Pre-Dispense Authorizations (PDAs)

a. PDAs provided on first pharmacy attempt (i.e., Number of

PDAs that did not encounter any rejections prior to being authorized) and stratified by stakeholder type who entered testing and counseling information through the REMS website (e.g. certified pharmacy staff, prescriber designees, REMS contact center staff, healthcare providers)

b. Total number of authorizations that encountered one or more PDA rejections; provide the reasons for such rejections and stratified by stakeholder type who entered testing and counseling information through the REMS website (e.g. certified pharmacy staff, prescriber designees, REMS contact center staff, healthcare providers)

Health Outcomes and/or Surrogates of Health Outcomes

12. Hepatic Adverse Events (provide previous, current and cumulative reporting periods)

Each manufacturer will provide in their submission an analysis of all cases of a serious hepatic event 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

13. Pregnancy Cases (provide previous, current and cumulative reporting periods)

Each manufacturer will provide in their submission an analysis of all cases of pregnancy reported in association with bosentan from any source including but not limited to the following:

a. The number of pregnancy exposures reported and stratified by source of exposure report (i.e. spontaneous report, reported via the REMS Program, etc.)

b. Pregnancy rate. Include incidence rates (in person-years) for pregnancy cases to allow comparison with expected rates in the general population.

c. A cumulative summary of U.S. pregnancy cases should be provided in the assessment reports. Worldwide pregnancy cases will be provided in periodic reports (e.g., PBRERs) by applicable Applicant-(s). At a minimum, the summary of pregnancy cases in the assessment reports will include but not be limited to the following information:
   i. Event identification number
   ii. Indication for bosentan
   iii. Contraceptive methods used
   iv. Root cause of contraception failure
   v. Weeks gestation at termination if pregnancy terminated
   vi. Outcome for each pregnancy
   vii. Age of patient

d. Follow-up of outstanding pregnancy reports from the previous assessment reporting period

e. Root cause analysis of each reported pregnancy to determine the reason the REMS program failed to prevent the pregnancy exposure. This root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis.

Knowledge

14. **Evaluation of Knowledge of the Bosentan REMS Program and Risks of Bosentan/Surveys** (Provide for each reporting period)

a. An evaluation of certified prescribers' knowledge of:
   i. the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan,
   ii. the need to monitor patients at baseline and monthly,
   iii. the need to counsel patients about the risks and monitoring,

iv. the need to enroll patients in the Bosentan REMS program
v. identification of any burdens to the healthcare system as a result of the REMS

b. An evaluation of pharmacy authorized representatives' and trained pharmacists' knowledge of:
   i. the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan
   ii. the need to confirm that appropriate patient monitoring and counseling occur before dispensing bosentan
   iii. identification of any burdens to the healthcare system as a result of the REMS

c. An evaluation of patients' knowledge of:
   i. the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan,
   ii. appropriate baseline and monthly monitoring, ~~and~~
   iii. appropriate contraception
   iv. identification of any burden or difficulties in accessing care as a result of the REMS

15. Overall Assessment of REMS

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

(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 and NDA 209279 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 021290 and NDA 209279 CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

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

or

NEW SUPPLEMENT FOR NDA 021290 and 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 and 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 and 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.

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, call Lori Anne Wachter, RN, BSN RAC-drugs (US), Regulatory Project Manager for Safety, at 301 796-3975.

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, PharmD.
Deputy Director for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

ENCLOSURE(S):
- 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/

MARY R SOUTHWORTH
04/29/2022 05:04:50 PM