CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021290Orig1s043

Trade Name:	TRACLEER
Generic or Proper Name:	(bosentan)
Sponsor:	Actelion Pharmaceuticals Inc.
Approval Date:	April 29, 2022
Indication:	Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1): • in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). • in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

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021290Orig1s043

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APPLICATION NUMBER:

021290Orig1s043

APPROVAL LETTER

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021290Orig1s043

REMS

Risk Evaluation and Mitigation Strategy (REMS) Document
Bosentan Shared System REMS

I. Administrative Information

Initial Shared System REMS Approval: 04/2019
Most Recent REMS Update: 04/2022

II. REMS Goal

The goal of the Bosentan REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan by:

1. Ensuring prescribers are educated on the following:
   - the risks of hepatotoxicity and embryo-fetal toxicity
2. Ensuring prescribers are educated on and adhere to the following:
   - counseling patients about these risks and the need for monthly monitoring
   - enrolling patients in the Bosentan REMS
   - monitoring patients at baseline and monthly
3. Ensuring that pharmacies are educated on the following:
   - the risks of hepatotoxicity and embryo-fetal toxicity
4. Ensuring that pharmacies are educated on and adhere to the following:
   - confirming that the appropriate patient monitoring and counseling has occurred before dispensing bosentan
5. Ensuring that patients are informed about:
   - the risks of hepatotoxicity and embryo-fetal toxicity
   - appropriate baseline and monthly patient monitoring
   - appropriate contraception

III. REMS Requirements

The Bosentan Applicants must ensure that healthcare providers, patients, pharmacies, and wholesalers-distributors comply with the following requirements:

1. Healthcare Providers who prescribe bosentan must:

To become certified to prescribe	1. Review the drug's Prescribing Information. 2. Review the Prescriber Guide. 3. Enroll in the REMS by completing the Prescriber Enrollment Form and submitting it to the REMS Program.
Before treatment initiation (first dose)	4. For all patients: Counsel the patient on the risk of hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity, to contact the prescriber if the patient has any signs or symptoms of liver problems, and REMS Program requirements including the need to complete liver testing using the Guide for Patients. 5. For all patients: Assess the patient's liver function. Document and submit to the REMS Program using the Patient Enrollment Form.

	6. For all females: Assess the patient's reproductive status using the definitions in the Prescriber Guide. Document and submit to the REMS Program using the Patient Enrollment Form. 7. For pre-pubertal females: Counsel the patient about the risk of embryo-fetal toxicity and the need to immediately contact the prescriber when the patient begins to menstruate using the Guide for Patients. 8. For females of reproductive potential: Counsel the patient about the risk of embryo-fetal toxicity, the need to use reliable contraception as defined in the Prescriber Guide during treatment and for one month following treatment discontinuation, the need to complete pregnancy testing, the need to contact the prescriber if pregnancy is suspected, and emergency contraception using the Guide for Patients. 9. For females of reproductive potential: Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results. Document and submit to the REMS Program using the Patient Enrollment Form. 10. Provide the patient with the Guide for Patients. 11. Enroll the patient by completing the Patient Enrollment Form and submitting it to the REMS Program. Provide a completed copy of the form to the patient.
During treatment; monthly	12. For all patients: Assess the patient's liver function and counsel the patient on the risk of hepatotoxicity. 13. For females of reproductive potential: Counsel the patient on the risk of embryo-fetal toxicity. 14. For females of reproductive potential: Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results.
During treatment; at least annually	15. For pre-pubertal females age 8 years or older: Document reproductive status and submit to the REMS Program using the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form.
After treatment discontinuation; for one month	16. For females of reproductive potential: Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results.
At all times	17. Report adverse events suggestive of hepatotoxicity to the REMS Program. 18. Report pregnancies to the REMS Program. 19. For pre-pubertal females: Assess the patient's reproductive status.
At all times, within 10 business days	20. Report a change or misclassification in reproductive status to the REMS Program using the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form.

2. Females of reproductive potential who are prescribed bosentan:

Before treatment initiation	1. Review the Guide for Patients. 2. Get a liver test and a pregnancy test. 3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. 4. Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if you have any signs or symptoms of liver problems, the need to complete liver testing, the risk of serious birth defects, the need to use reliable contraception during treatment and for one month following treatment discontinuation, the need to complete pregnancy testing, the need to contact the prescriber if you suspect you are pregnant, and emergency contraception using the Guide for Patients.
During treatment; before each prescription	5. Get a liver test and a pregnancy test. 6. Adhere to the safe use condition: Communicate with the REMS Program or pharmacy to confirm completion of pregnancy testing and liver testing. 7. Receive counseling from the prescriber or pharmacy on the risks of liver problems and serious birth defects associated with bosentan treatment.
During treatment and after treatment discontinuation for one month	8. Adhere to the safe use condition: Use reliable contraception as described in the Guide for Patients.
After treatment discontinuation; one month	9. Get a pregnancy test.
At all times	10. Inform the prescriber if you have any signs or symptoms of liver problems as described in the Guide for Patients. 11. Inform the prescriber immediately if you suspect you may be pregnant.

3. Pre-pubertal females who are prescribed bosentan:

Before treatment initiation	1. Review the Guide for Patients. 2. Get a liver test. 3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. 4. Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if you have any signs or symptoms of liver problems, the need to complete liver testing, the risk of serious birth defects, and the need to contact the prescriber when you begin to menstruate using the Guide for Patients.

During treatment; before each prescription	5. Get a liver test. 6. Adhere to the safe use condition: Communicate with the REMS Program or pharmacy to confirm completion of liver testing. 7. Receive counseling from the prescriber or pharmacy on the risks of liver problems and serious birth defects associated with bosentan treatment.
At all times	8. If over the age of 8: Be monitored for a change in reproductive status. 9. Inform the prescriber if you have any signs or symptoms of liver problems as described in the Guide for Patients. 10. Inform the prescriber if there is a change in reproductive status.

4. Post-menopausal females or females with other medical reasons for permanent, irreversible infertility who are prescribed bosentan:

Before treatment initiation	1. Review the Guide for Patients. 2. Get a liver test. 3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. 4. Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if you have any signs or symptoms of liver problems, and the need to complete liver testing using the Guide for Patients.
During treatment; before each prescription	5. Get a liver test. 6. Adhere to the safe use condition: Communicate with the REMS Program or pharmacy to confirm completion of liver testing. 7. Receive counseling from the prescriber or pharmacy on the risk of liver problems associated with bosentan treatment.
At all times	8. Inform the prescriber if you have any signs or symptoms of liver problems as described in the Guide for Patients. 9. Inform the prescriber if there is a change in reproductive status.

5. Males who are prescribed bosentan:

Before treatment initiation	1. Review the Guide for Patients. 2. Get a liver test. 3. Enroll in the REMS Program by completing the Patient Enrollment Form with the prescriber. Enrollment information will be provided to the REMS Program. 4. Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if you have any signs or symptoms of liver problems, and the need to complete liver testing using the Guide for Patients.

During treatment; before each prescription	5. Get a liver test. 6. Adhere to the safe use condition: Communicate with the REMS Program or pharmacy to confirm completion of liver testing. 7. Receive counseling from the prescriber or pharmacy on the risk of liver problems associated with bosentan treatment.
At all times	8. Inform the prescriber if you have any signs or symptoms of liver problems as described in the Guide for Patients.

6. Outpatient pharmacies that dispense bosentan must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative review the Pharmacy Guide. 3. Have the authorized representative enroll in the REMS Program by completing the Outpatient Pharmacy Enrollment Form or Chain Pharmacy Headquarters Enrollment Form and submitting it to the REMS Program. 4. Train all relevant staff involved in dispensing bosentan on the REMS Program requirements using the Pharmacy Guide.
Before dispensing	5. For all patients: Obtain authorization to dispense each prescription by contacting the REMS Program to verify the patient is enrolled, the prescriber is certified, the pharmacy is certified, if counseling is complete, liver testing is complete, the reproductive status has not changed for female patients, and the pregnancy test is completed for females of reproductive potential or the prescriber authorizes the refill. 6. For patients without documented testing: Communicate with the patient or prescriber to confirm testing. Document and submit the confirmation of testing using the REMS Program website or Contact Center. 7. For all patients without documented counseling on hepatotoxicity: Counsel the patient on the risk of hepatotoxicity. Document and submit the confirmation of counseling using the REMS Program website or Contact Center. 8. For females of reproductive potential and pre-pubertal females without documented counseling on embryo-fetal toxicity: Counsel the patient on the risk of embryo-fetal toxicity. Document and submit the confirmation of counseling using the REMS Program website or Contact Center. 9. Dispense no more than a 30 days' supply.
To maintain certification to dispense	10. Have the new authorized representative certify in the REMS Program by completing the Outpatient Pharmacy Enrollment Form or Chain Pharmacy Headquarters Enrollment Form if the authorized representative changes.
At all times	11. Report adverse events suggestive of hepatotoxicity to the REMS Program.

	12. Report pregnancies to the REMS Program. 13. Do not distribute, transfer, loan, or sell bosentan, except to certified dispensers. 14. Maintain records of dispensing. 15. Maintain records of training. 16. Maintain records that all processes and procedures are in place and are being followed. 17. Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

7. Inpatient pharmacies that dispense bosentan must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy. 2. Have the authorized representative review the Pharmacy Guide. 3. Have the authorized representative enroll in the REMS Program by completing the Inpatient Pharmacy Enrollment Form and submitting it to the REMS Program. 4. Train all relevant staff involved in dispensing bosentan on the REMS Program requirements using the Pharmacy Guide. 5. Establish processes and procedures to verify the patient is enrolled or will be enrolled prior to discharge, the patient is under the care of a certified prescriber, counseling is complete, and liver testing is complete. 6. For females of reproductive potential: Establish processes and procedures to verify pregnancy testing is complete and counseling on embryo-fetal toxicity is complete.
Before dispensing	7. For all patients: Verify the patient is enrolled or will be prior to discharge, the patient is under the care of a certified prescriber, the pharmacy is certified, counseling on the risk of hepatotoxicity is complete, and that liver testing is complete. 8. For females of reproductive potential: Verify that pregnancy testing is complete and counseling on embryo-fetal toxicity is complete.
At discharge	9. Dispense no more than a 15 days' supply.
To maintain certification to dispense	10. Have the new authorized representative certify in the REMS Program by completing the Inpatient Pharmacy Enrollment Form if the authorized representative changes.
At all times	11. Report adverse events suggestive of hepatotoxicity to the REMS Program. 12. Report pregnancies to the REMS Program. 13. Do not distribute, transfer, loan, or sell bosentan, except to certified dispensers. 14. Maintain records of training. 15. Maintain records that all processes and procedures are in place and are being followed. 16. Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

8. Wholesalers-distributors that distribute bosentan must:	
To be able to distribute	1. Establish processes and procedures to ensure that bosentan is distributed only to certified pharmacies. 2. Train all relevant staff involved in distribution on the REMS Program requirements.
At all times	3. Distribute only to certified pharmacies. 4. Maintain records of drug distribution. 5. Maintain records that all processes and procedures are in place and are being followed. 6. Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

Bosentan Applicants must provide training to healthcare providers who prescribe bosentan.

The training includes the following educational material: Prescriber Guide. The training must be available online and hard copy format via fax or mail.

Bosentan Applicants must provide training to pharmacies that dispense bosentan.

The training includes the following educational material: Pharmacy Guide. The training must be available online and hard copy format via fax or mail.

To support REMS Program operations, Bosentan Applicants must:

1. Authorize the initial (first dose) dispensing for each patient based on receipt of a Patient Enrollment Form and verifying that the prescriber is certified and the pharmacy is certified. If the Patient Enrollment Form is not complete, the patient is not authorized to receive drug until the completed form is received.
   For subsequent dispensings: authorize dispensing based on verifying the patient is enrolled, the prescriber is certified, the pharmacy is certified, if counseling is complete, liver testing is complete, the reproductive status has not changed for female patients, and the pregnancy test is complete for females of reproductive potential or the prescriber authorizes the refill. The patient is not authorized to receive drug until all verification components are complete.
2. Establish and maintain a REMS Website, www.BosentanREMSProgram.com. The REMS Website must include the capability to complete prescriber and pharmacy certification online, the capability to enroll and manage patients online, the capability to verify prescriber certification and patient enrollment online, and the option to print the Prescribing Information, Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Website. The REMS Website must not link back to the promotional product website(s).
3. Make the REMS Website fully operational and all REMS materials available through the REMS Website and Contact Center within 60 calendar days of REMS modification (04/29/2022).
4. Establish and maintain a Contact Center for REMS participants at 1-866-359-2612.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and certified in the REMS.

6. Ensure prescribers and pharmacies are able to complete the certification process online, by fax and mail.
7. Notify prescribers and pharmacies within two business days after they become certified in the REMS Program.
8. Ensure prescribers are able to complete the patient enrollment process online, by fax and mail.
9. Ensure prescribers are able to confirm liver testing, pregnancy testing (as appropriate), and counseling online and by fax by using the Testing and Patient Counseling Reporting Form.
10. Ensure prescribers are able to report change in patient reproductive status online and by fax.
11. Ensure pharmacies are able to document confirmation of liver and pregnancy testing by phone and online.
12. Ensure pharmacies are able to document confirmation of counseling by phone and online.
13. Ensure pharmacies are able to obtain authorization to dispense by phone and online.
14. Ensure the Contact Center or the outpatient pharmacy confirms completion of liver testing, counseling, and pregnancy testing (as appropriate) on a monthly basis if the Testing and Patient Counseling Reporting Form has not been received.
15. Ensure the Contact Center reminds prescribers who cannot confirm that testing was completed of the requirement to order and review monthly liver tests and pregnancy tests.
16. Ensure that the Contact Center contacts the prescriber of a pre-pubertal female annually to have the prescriber verify the pre-pubertal female's reproductive status by completing the Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form.
17. Ensure the Contact Center updates the database of a patient's change in reproductive status within one business day of receipt of a completed Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form.
18. Ensure pharmacies are able to certify as inpatient (including, but not limited to, pharmacies in hospitals, long-term care facilities, prisons, and state psychiatric units) or outpatient pharmacies.
19. Provide certified prescribers access to the database of certified pharmacies and enrolled patients.
20. Provide certified pharmacies access to the database of certified prescribers and enrolled patients.
21. Provide the Prescriber Enrollment Form, Prescriber Guide, Fact Sheet, Patient Enrollment Form, Guide for Patients, and the Testing and Patient Counseling Reporting Form to prescribers who (1) attempt to prescribe bosentan and are not yet certified or (2) inquire about how to become certified.

To ensure REMS participants' compliance with the REMS Program, Bosentan Applicants must:

22. Verify the name and contact information of the pharmacy's authorized representative every 2 years. If different than the current authorized representative on file, the pharmacy is required to certify with a new authorized representative.
23. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: bosentan distribution and dispensing; certification of prescribers and pharmacies; authorized wholesalers-distributors; enrolled patients; and audits of certified pharmacies and authorized wholesalers-distributors. These records must be readily available for FDA inspections.
24. Establish a plan for addressing noncompliance with REMS Program requirements.
25. Establish and maintain an ongoing annual audit plan for pharmacies and wholesalers-distributors.
26. Monitor prescribers, pharmacies, and wholesalers-distributors on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if noncompliance is identified, including de-certification.
27. Audit 10 pharmacies or one percent (1%), whichever is greater, of the certified pharmacies within 180 calendar days after the pharmacy places its first order of bosentan and maintain an ongoing audit plan for pharmacies to ensure that all processes and procedures are in place and functioning to support the requirements of the Bosentan REMS. Bosentan Applicants must institute corrective action if noncompliance is identified.
28. Audit wholesalers-distributors within 180 calendar days after the wholesaler-distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Bosentan REMS. The wholesaler-distributor must also be included in the Bosentan Applicants ongoing annual audit plan. Bosentan Applicants must institute corrective action if noncompliance is identified.
29. Take reasonable steps to improve implementation of and compliance with the requirements in the Bosentan REMS based on monitoring and evaluation of the Bosentan REMS.

IV. REMS Assessment Timetable

Bosentan NDA Applicants must submit REMS Assessments annually from the date of the initial approval of the Bosentan REMS (04/26/2019). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Bosentan NDA Applicants must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the Bosentan REMS and are appended:

Enrollment Forms:

Prescriber:

1. Prescriber Enrollment Form

Patient:

2. Patient Enrollment Form

Pharmacy:

3. Outpatient Pharmacy Enrollment Form
4. Chain Pharmacy Headquarters Enrollment Form
5. Inpatient Pharmacy Enrollment Form

Training and Educational Materials

Prescriber:

6. Prescriber Guide
7. Fact Sheet

Pharmacy:

8. Pharmacy Guide

Patient:

9. Guide for Patients

Patient Care Forms

10. Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form
11. Testing and Patient Counseling Reporting Form

Other Materials

12. REMS Website

Bosentan
REMS Program

Prescriber Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Instructions

For immediate certification, please go to www.BosentanREMSProgram.com. Scan the Quick Response (QR) code to complete the form online.

To submit this form via fax or mail, please complete all required fields below and fax to 1-800-730-8231 or mail to the Bosentan REMS, 200 Pinecrest Plaza Morgantown, WV 26505. Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit **www.BosentanREMSProgram.com**, or call the Bosentan REMS at 1-866-359-2612.

Prescriber Responsibilities

By signing this form, I agree to comply with the following Bosentan REMS requirements:

- Reviewing the Prescribing Information and the **Prescriber Guide**.
- Enrolling in the Bosentan REMS by completing the **Prescriber Enrollment Form** and submitting it to the Bosentan REMS.

Before treatment initiation (first dose), I must:

For all patients:

- Provide the patient a copy of the **Guide for Patients**.
- Enroll the patient by completing and submitting the **Patient Enrollment Form** to the Bosentan REMS. Provide a completed copy to the patient.
- Counsel the patient on the risk of hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity, to contact the prescriber if the patient has any signs or symptoms of liver problems, and program requirements including the need to complete liver testing using the **Guide for Patients**.
- Assess the patient's liver function. Document and submit to the Bosentan REMS using the **Patient Enrollment Form**.

For all females:

- Assess the patient's reproductive status using the definitions in the **Prescriber Guide**. Document and submit to the Bosentan REMS using the **Patient Enrollment Form**.

For pre-pubertal females:

- Counsel the patient about the risk of embryo-fetal toxicity and the need to immediately contact the prescriber when the patient begins to menstruate using the **Guide for Patients**.

For females of reproductive potential:

- Counsel the patient about the risk of embryo-fetal toxicity, the need to use reliable contraception as defined in the **Prescriber Guide** during treatment and for one month following treatment discontinuation, the need to complete pregnancy testing, the need to contact the prescriber if pregnancy is suspected, and emergency contraception using the **Guide for Patients**.
- Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results. Document and submit to the Bosentan REMS using the **Patient Enrollment Form**.

During treatment; monthly, I must:

For all patients:

- Assess the patient's liver function and counsel the patient on the risk of hepatotoxicity.

For females of reproductive potential:

- Counsel the patient on the risk of embryo-fetal toxicity.
- Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results.

During treatment; at least annually, I must:

For pre-pubertal females age 8 years or older:

- Document reproductive status and submit to the Bosentan REMS using the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**.

After treatment discontinuation; for one month, I must:

For females of reproductive potential:

- Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results.

At all times, I must:

- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.

For pre-pubertal females:

- Assess the patient's reproductive status.

At all times, within 10 business days, I must:

- Report a change or misclassification in reproductive status to the Bosentan REMS using the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**.

Prescriber Information (All fields required unless otherwise indicated)

First Name: MI (optional): Last Name:

Email: Professional Designation (select one): ❒ MD ❒ DO ❒ PA ❒ NP

NPI#: Medical Specialty (select one): ❒ Cardiology ❒ Pulmonology ❒ Rheumatology ❒ General/Family Practice ❒ Other

Clinic/Practice Name:

Address: City:

State: Zip Code: Preferred Method of Contact (select one): ❒ Fax ❒ Email

Office Phone: Ext (optional): Fax:

Mobile:

Prescriber Signature

By signing below, you signify your understanding of the risks of bosentan treatment and your obligations as a bosentan prescriber to educate your patients about the Bosentan REMS, monitor them appropriately, and report adverse events suggestive of hepatotoxicity and pregnancies to the Bosentan REMS.

Signature: **Date**

Reference ID: 4976585

Bosentan
REMS Program

Patient Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Instructions

For immediate patient enrollment, please go to www.BosentanREMSProgram.com. Scan the Quick Response (QR) code to complete the form online. The patient must complete this form with the prescriber.

To submit this form via fax or mail, please complete all required fields below and fax to 1-800-730-8231 or mail to the Bosentan REMS, 200 Pinecrest Plaza Morgantown, WV 26505.

If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit **www.BosentanREMSProgram.com**, or call the Bosentan REMS at 1-866-359-2612.

Patient Agreement and Signature

To become enrolled in the Bosentan REMS, a patient and/or parent/legal guardian is indicating that:

FEMALES OF REPRODUCTIVE POTENTIAL

Before treatment, I must:

- Review the **Guide for Patients**.
- Get a liver test and a pregnancy test.
- Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS.
- Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, the need to complete liver testing, the risk of serious birth defects, the need to use reliable contraception during treatment and for one month following treatment discontinuation, the need to complete pregnancy testing, the need to contact the prescriber if I suspect I am pregnant, and emergency contraception using the **Guide for Patients**.

During treatment, before each prescription, I must:

- Get a liver test and a pregnancy test.
- Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of pregnancy testing and liver testing.
- Receive counseling from the prescriber or pharmacy on the risks of liver problems and serious birth defects associated with bosentan treatment.

During treatment and after treatment discontinuation for one month, I must:

- Adhere to the safe use condition: Use reliable contraception as described in the **Guide for Patients**.

After treatment discontinuation for one month, I must:

- Get a pregnancy test.

At all times, I must:

- Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients**.
- Inform the prescriber immediately if I suspect I may be pregnant.

PRE-PUBERTAL FEMALES

Before treatment, I must:

- Review the **Guide for Patients**.
- Get a liver test.
- Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS.
- Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, the need to complete liver testing, the risk of serious birth defects, and the need to contact the prescriber when I begin to menstruate using the **Guide for Patients**.

During treatment, before each prescription, I must:

- Get a liver test.
- Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of liver testing.
- Receive counseling from the prescriber or pharmacy on the risks of liver problems and serious birth defects associated with bosentan treatment.

At all times, I must:

- If over the age of 8: Be monitored for a change in reproductive status.
- Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients**.
- Inform the prescriber if I have a change in reproductive status.

POST-MENOPAUSAL FEMALES OR FEMALES WITH OTHER MEDICAL REASONS FOR PERMANENT, IRREVERSIBLE INFERTILITY

Before treatment, I must:

- Review the **Guide for Patients**.
- Get a liver test.
- Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS.
- Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, and the need to complete liver testing using the **Guide for Patients**.

Reference ID: 4976585

Patient Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

During treatment, before each prescription, I must:

- Get a liver test.
- Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of liver testing.
- Receive counseling from the prescriber or pharmacy on the risk of liver problems associated with bosentan treatment.

At all times, I must:

- Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients.**
- Inform the prescriber if I have a change in reproductive status.

MALES

Before treatment, I must:

- Review the **Guide for Patients**.
- Get a liver test.
- Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS.
- Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, and the need to complete liver testing using the **Guide for Patients**.

During treatment, before each prescription, I must:

- Get a liver test.
- Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of liver testing.
- Receive counseling from the prescriber or pharmacy on the risk of liver problems associated with bosentan treatment.

At all times, I must:

- Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients**.

Patient Information (All fields required unless otherwise indicated)

First Name:	MI (optional):	Last Name:	Gender: ❒ Female ❒ Male
Date of Birth (MM/DD/YYYY):		Email (optional):	
Primary Phone #:		Alternate Phone # (optional):	
Address:		City:	
State:		Zip Code:	
Parent/Legal Guardian (optional):		Relationship (optional):	

By signing below, you attest that you understand the requirements of the Bosentan REMS as indicated on this form and in the ***Guide for Patients***, and you will follow the requirements of the Bosentan REMS.

Patient/Parent/Legal Guardian Signature: **Date:**

Patient Reproductive Classification and Acknowledgement of Counseling (To be completed by the prescriber)

For this patient, have you reviewed their current liver tests? ❒ Yes ❒ No

If your patient is FEMALE, select the correct female patient category (please see definitions of these terms in the *Prescriber Guide*):

❒ Female of Reproductive Potential

If this patient is a female of reproductive potential, has a negative pregnancy test been completed prior to prescribing bosentan?
❒ Yes ❒ No

❒ Female of Non-Reproductive Potential

Please specify:
❒ Pre-pubertal Female ❒ Post-menopausal Female
❒ Female with other medical reasons for permanent, irreversible infertility

For this patient, have you provided counseling on the risks associated with bosentan treatment and the Bosentan REMS requirements? ❒ Yes ❒ No

Prescriber Information (All fields required unless otherwise indicated)

First Name:	MI (optional):	Last Name:
NPI#:		
Address:		City:
State:		Zip Code:
Phone:	Ext (optional):	Fax:

Prescriber Signature

By signing below, you attest that the patient indicated on this form meets the reproductive potential classification as defined in the ***Prescriber Guide***, and that you agree to follow the requirements of the Bosentan REMS.

Prescriber Signature: **Date:**

Bosentan
REMS Program

Outpatient Pharmacy Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Instructions

For immediate enrollment, please go to www.BosentanREMSProgram.com. Scan the Quick Response (QR) code to complete the form online.

To submit this form via fax or mail, please complete all required fields below and fax to 1-800-730-8231 or mail to the Bosentan REMS, 200 Pinecrest Plaza Morgantown, WV 26505. Upon completion of these steps, the Bosentan REMS will notify you of successful certification. If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit **www.BosentanREMSProgram.com**, or call the Bosentan REMS at 1-866-359-2612.

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to oversee implementation of and compliance with the Bosentan REMS. I attest to understanding the Bosentan REMS requirements, and accept responsibility to:

As the Authorized Pharmacy Representative, I must:

- Review the **Pharmacy Guide**.
- Enroll in the Bosentan REMS by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the Bosentan REMS.
- Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the **Pharmacy Guide**.

Before dispensing, my pharmacy must:

For all patients:

- Obtain authorization to dispense each prescription by contacting the Bosentan REMS to verify:
  - the patient is enrolled,
  - the prescriber is certified,
  - the pharmacy is certified,
  - if counseling is complete,
  - liver testing is complete,
  - the reproductive status has not changed for female patients, and
  - the pregnancy test is completed for females of reproductive potential or the prescriber authorizes the refill.
- Dispense no more than a 30 days' supply.

For patients without documented testing:

- Communicate with the patient or prescriber to confirm testing.
- Document and submit the confirmation of testing using the Bosentan REMS Website or by calling the Contact Center.

For all patients without documented counseling on hepatotoxicity:

- Counsel the patient on the risk of hepatotoxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

For females of reproductive potential and pre-pubertal females without documented counseling on embryo-fetal toxicity:

- Counsel the patient on the risk of embryo-fetal toxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

At all times my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.
- Not distribute, transfer, loan, or sell bosentan, except to certified dispensers.
- Maintain records of
  - dispensing,
  - training, and
  - that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.
- Have the new authorized representative certify in the Bosentan REMS by completing the **Outpatient Pharmacy Enrollment Form** if the authorized representative changes.

Pharmacy Information (All fields required)

Pharmacy Name:			
Pharmacy Identifiers:	NCPDP:	NPI:	DEA:
Address:		City:	
State:		Zip Code:	
Phone:		Fax:	

Continued on the following page.

Reference ID: 4976585

Bosentan
REMS Program

Outpatient Pharmacy Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Authorized Representative Information (All fields required)

First Name: Last Name:

Credentials (select one): ❒ RPh ❒ PharmD ❒ BCPS ❒ Other

Office Phone: Fax: Email:

Preferred Method of Contact (select one): ❒ Fax ❒ Email

Authorized Representative Signature

By signing below, you signify your understanding of the risks of bosentan treatment, your obligations as a pharmacy certified in the Bosentan REMS as outlined above, and you agree to oversee the implementation of and compliance with the Bosentan REMS requirements for this pharmacy.

Signature: **Date:**

Reference ID: 4976585

Bosentan
REMS Program

Chain Pharmacy Headquarters Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Instructions

For immediate enrollment, please go to www.BosentanREMSProgram.com. Scan the Quick Response (QR) code to complete the form online.

To submit this form via fax or mail, please complete all required fields below and fax to 1-800-730-8231 or mail to the Bosentan REMS 200 Pinecrest Plaza Morgantown, WV 26505. Upon completion of these steps, the Bosentan REMS will notify you of successful certification. If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit **www.BosentanREMSProgram.com**, or call the Bosentan REMS at 1-866-359-2612.

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to oversee implementation of and compliance with the Bosentan REMS. I attest to understanding the Bosentan REMS requirements, and accept responsibility to:

As the Authorized Pharmacy Representative, I must:

- Review the **Pharmacy Guide**.
- Enroll in the Bosentan REMS by completing the **Chain Pharmacy Headquarters Enrollment Form** and submitting it to the Bosentan REMS.
- Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the **Pharmacy Guide** and report confirmation of training for each dispensing location to the Bosentan REMS.

Before dispensing, my pharmacy must:

For all patients:

- Obtain authorization to dispense each prescription by contacting the Bosentan REMS to verify:
  - the patient is enrolled,
  - the prescriber is certified,
  - the pharmacy is certified,
  - if counseling is complete,
  - liver testing is complete,
  - the reproductive status has not changed for female patients, and
  - the pregnancy test is completed for females of reproductive potential or the prescriber authorizes the refill.
- Dispense no more than a 30 days' supply.

For patients without documented testing:

- Communicate with patient or prescriber to confirm testing.
- Document and submit the confirmation of testing using the Bosentan REMS Website or by calling the Contact Center.

For all patients without documented counseling on hepatotoxicity:

- Counsel the patient on the risk of hepatotoxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

For females of reproductive potential and pre-pubertal females without documented counseling on embryo-fetal toxicity:

- Counsel the patient on the risk of embryo-fetal toxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

At all times my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.
- Not distribute, transfer, loan, or sell bosentan, except to certified dispensers.
- Maintain records of
  - dispensing,
  - training, and
  - that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.
- Have the new authorized representative certify in the Bosentan REMS by completing the **Chain Pharmacy Headquarters Enrollment Form** if the authorized representative changes.

Chain Pharmacy Headquarters Information (All fields required)

Pharmacy Name:	
Address:	City:
State:	Zip Code:
Phone:	Fax:

Continued on the following page.

Reference ID: 4976585

Bosentan
REMS Program

Chain Pharmacy Headquarters Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Authorized Representative Information (All fields required)

First Name: Last Name:

Credentials (select one): ❒ RPh ❒ PharmD ❒ BCPS ❒ Other

Office Phone: Fax: Email:

Preferred Method of Contact (select one): ❒ Fax ❒ Email

Authorized Representative Signature

By signing below, you signify your understanding of the risks of bosentan treatment, your obligations as a pharmacy certified in the Bosentan REMS as outlined above, and you agree to oversee the implementation of and compliance with the Bosentan REMS requirements for this pharmacy.

Signature: **Date:**

Next Steps

1. After completing and signing this form, please fax to 1-800-730-8231 or mail to the Bosentan REMS, 200 Pinecrest Plaza Morgantown, WV 26505
2. Once this form is processed, you will receive a pharmacy certification confirmation. Upon receipt, your chain pharmacy headquarters is certified and your dispensing locations are now eligible to complete their training
3. Once each dispensing location is trained, it is your responsibility to report confirmation of training to the Bosentan REMS online through **www.BosentanREMSProgram.com**, or by calling the Contact Center at 1-866-359-2612 to obtain instructions on providing a list of trained pharmacy locations. Once the Bosentan REMS confirms the required dispensing information, the dispensing location will be authorized to purchase, receive, and dispense bosentan

Bosentan
REMS Program

Inpatient Pharmacy Enrollment Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Instructions

For immediate enrollment, please go to www.BosentanREMSProgram.com. Scan the Quick Response (QR) code to complete the form online.

To submit this form via fax or mail, please complete all required fields below and fax to 1-800-730-8231 or mail to the Bosentan REMS, 200 Pinecrest Plaza Morgantown, WV 26505. Upon completion of these steps, the Bosentan REMS will notify you of successful certification. If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit **www.BosentanREMSProgram.com**, or call the Bosentan REMS at 1-866-359-2612.

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to oversee implementation of and compliance with the Bosentan REMS. I attest to understanding the Bosentan REMS requirements, and accept responsibility to:

As the Authorized Pharmacy Representative, I must:

- Review the **Pharmacy Guide**.
- Enroll in the Bosentan REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the Bosentan REMS.
- Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the **Pharmacy Guide**.
- Establish processes and procedures to verify:
  - the patient is enrolled or will be enrolled prior to discharge,
  - the patient is under the care of a certified prescriber,
  - counseling is complete,
  - liver testing is complete, and
  - pregnancy testing is complete (for females of reproductive potential).

Before dispensing, my pharmacy must:

- Verify the patient:
  - is enrolled or will be prior to discharge,
  - is under the care of a certified prescriber,
  - counseling is complete,
  - completed liver testing, and
  - completed pregnancy testing (for females of reproductive potential).

At all times, my pharmacy must:

- Have the new authorized representative certify in the Bosentan REMS by completing the **Inpatient Pharmacy Enrollment Form** if the authorized representative changes.
- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.
- Not distribute, transfer, loan, or sell bosentan, except to certified dispensers.
- Maintain records of training.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

At discharge, my pharmacy must:

- Dispense no more than a 15 days' supply.

Pharmacy Information (All fields required)

Institution or Healthcare Setting Name:			
Provide one of the following identifiers:	NCPDP:	NPI:	DEA:
Address:		City:	
State:		Zip Code:	
Phone:		Fax:	

Authorized Representative Information (All fields required)

First Name:			Last Name:	
Credentials (select one):	❒ RPh	❒ PharmD	❒ BCPS	❒ Other
Office Phone:		Fax:		Email:
Preferred Method of Contact (select one):	❒ Fax	❒ Email		

Authorized Representative Signature

By signing below, you signify your understanding of the risks of bosentan treatment, your obligations as a pharmacy certified in the Bosentan REMS as outlined above, and you agree to oversee the implementation of and compliance with the Bosentan REMS requirements for this pharmacy.

Signature:	**Date:**

Reference ID: 4976585

Bosentan

REMS Program

Prescriber Guide

The Bosentan **R**isk **E**valuation and **M**itigation **S**trategy (REMS) is a single shared system for brand and generic bosentan medication for the treatment of pulmonary arterial hypertension (PAH). Due to the risks of hepatotoxicity and embryo-fetal toxicity, bosentan is only available through the Bosentan REMS.

- This guide contains important information for prescribers about the risks of bosentan, including hepatotoxicity and embryo-fetal toxicity, and includes: Bosentan REMS Overview
- Overview of Enrollment Requirements for Prescribers
- Bosentan Liver Testing Results and Monitoring Recommendations
- Prescriber's Role in the Bosentan REMS: Step by Step
- Contraception Options for Females of Reproductive Potential

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About Bosentan

Tracleer® (bosentan) is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).
- in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

Bosentan is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).

Risk of Hepatotoxicity

Bosentan may cause liver problems. Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.

Changes in aminotransferases may occur early or late in treatment. There have been rare postmarketing reports of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring; the contribution of bosentan could not be excluded.

Elevations in aminotransferases require close attention. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. See the Bosentan Liver Test Results and Monitoring Recommendations table on Page 9 for treatment and monitoring recommendations for liver enzyme elevations. Use of bosentan should generally be avoided in patients with elevated aminotransferases (>3 × ULN) **at baseline** because monitoring for hepatotoxicity may be more difficult.

Risk of Embryo-fetal Toxicity

Bosentan is contraindicated in females who are or may become pregnant and may cause fetal harm when administered to a pregnant woman. Animal studies have shown that bosentan is likely to cause major birth defects when administered during pregnancy. If bosentan is used during pregnancy, apprise the patient of the potential hazard to a fetus. To prevent pregnancy, females of reproductive potential must use reliable contraception prior to beginning treatment with bosentan, during treatment, and for one month following treatment discontinuation. Patients must not become pregnant while taking bosentan.

Bosentan REMS Overview

Due to the risks of hepatotoxicity and embryo-fetal toxicity, bosentan is only available through a single shared system required and approved by the Food and Drug Administration (FDA), called the Bosentan REMS. The Bosentan REMS is a single shared system including all brand and generic bosentan products.

The goal of the Bosentan REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan by:

- Ensuring prescribers are educated on the following:
  - the risks of hepatotoxicity and embryo-fetal toxicity
- Ensuring prescribers are educated on and adhere to the following:
  - counseling patients about these risks and the need for monthly monitoring
  - enrolling patients in the Bosentan REMS
  - monitoring patients at baseline and monthly
- Ensuring that pharmacies are educated on the following:
  - the risks of hepatotoxicity and embryo-fetal toxicity
- Ensuring that pharmacies are educated on and adhere to the following:
  - confirming that the appropriate patient monitoring and counseling has occurred before dispensing bosentan
- Ensuring that patients are informed about:
  - the risks of hepatotoxicity and embryo-fetal toxicity
  - appropriate baseline and monthly patient monitoring
  - appropriate contraception

The Bosentan REMS requirements:

- All healthcare providers must certify in the Bosentan REMS and must comply with the Bosentan REMS requirements in order to prescribe a bosentan product.
- All patients must be enrolled in the Bosentan REMS and must comply with the Bosentan REMS requirements in order to receive bosentan:
  - Patients must agree to complete liver tests and pregnancy tests (as appropriate based on the patient's reproductive potential classification) prior to receiving bosentan

  - All patients must agree to be counseled on the Bosentan REMS and the risks of treatment with bosentan
  - All patients must agree to be contacted about completing required monthly testing and counseling
- Prescribers must closely monitor transaminase levels and adjust monitoring and treatment with bosentan if increases are reported
- Prescribers must discontinue bosentan if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity or increases in bilirubin ≥2 x ULN, referenced on Page 9
- Only inpatient, outpatient, and chain pharmacies certified in the Bosentan REMS can dispense bosentan

Overview of Patient Enrollment Requirements for Prescribers

Requirement	All Patients	Females of Reproductive Potential	Females of Non-Reproductive Potential	
			Pre-pubertal	Post-menopausal or other medical reasons for permanent, irreversible infertility
Prescriber enrolls the patient into the Bosentan REMS	X			
Prescriber counsels the patient using the ***Guide for Patients***, particularly on the risks of hepatotoxicity and embryo-fetal toxicity and the need to use reliable contraception during treatment and for one month following treatment discontinuation	X*			
Prescriber orders and reviews liver tests prior to initiation of treatment and monthly during treatment	X			
Prescriber orders and reviews pregnancy tests prior to initiation of treatment, monthly during treatment, and for one month following treatment discontinuation		X		
Prescriber counsels the patient to contact the prescriber if they has any signs or symptoms of liver problems	X			
Prescriber counsels the patient to immediately contact the prescriber when the patient begins to menstruate			X	

Requirement	All Patients	Females of Reproductive Potential	Females of Non-Reproductive Potential	
			Pre-pubertal	Post-menopausal or other medical reasons for permanent, irreversible infertility
Prescriber counsels the patient to immediately contact the prescriber if the patient misses a menstrual period, suspects that they are pregnant, had unprotected sex, or thinks that their birth control has failed, and about the patient's medical options in the event of unprotected sexual intercourse or known or suspected contraception failure		X		
Prescriber verifies reproductive status annually in patients 8 years of age or older by completing the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***			X	
Prescriber completes the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** upon becoming aware of any change or misclassification in reproductive potential status within 10 business days of awareness		X	X	X

*For pre-pubertal female patients: Counsel only about the risks of hepatotoxicity, embryo-fetal toxicity, and the need to immediately contact the prescriber when the patient begins to menstruate.

Tracleer® and Bosentan Liver Test Results and Monitoring Recommendations

The tables below provide recommendations on managing patients taking Tracleer (Adult and Pediatric Patients) and bosentan (Patients >12 years) with elevated liver test results. Elevated monthly liver test results do not preclude treatment with Tracleer or bosentan.

- Table 1: Dosage Adjustment and Monitoring for **Tracleer**
- Table 2: Dosage Adjustment and Monitoring for **Bosentan**

Table 1. Dosage Adjustment and Monitoring for Patients Taking Tracleer Who Develop Aminotransferase Elevations >3 x ULN

ALT/AST level	Treatment and monitoring recommendations
>3 to ≤5 x ULN	**Confirm** by another aminotransferase test: **if confirmed**: ▪ in adults and pediatric patients >12 years and >40 kg, reduce the daily dose to 62.5mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values, treatment may continue or be reintroduced at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. ▪ in all other pediatric patients*, interrupt treatment with no prior dose reduction. If the aminotransferase levels return to pretreatment values, reintroduce at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
>5 to ≤8 x ULN	**Confirm** by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, ▪ in adults and pediatric patients >12 years and >40 kg, consider reintroduction of treatment at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. ▪ in all other pediatric patients*, consider reintroduction at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
>8 x ULN	**Stop** treatment permanently. There is no experience with reintroduction of Tracleer in these circumstances.

*Use of bosentan in pediatric patients ≤12 years of age is exclusive to Tracleer.

Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury, or increases in bilirubin of ≥2 x ULN.

Table 2. Dosage Adjustment and Monitoring for Patients >12 Years Taking Bosentan Who Develop Aminotransferase Elevations >3 x ULN

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	**Confirm** by another aminotransferase test; **if confirmed**, ▪ in patients >12 years and >40 kg, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values, treatment may continue or be reintroduced at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. ▪ in patients >12 years and <40 kg, interrupt treatment with no prior dose reduction. If the aminotransferase levels return to pretreatment values, reintroduce at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
> 5 and ≤ 8 x ULN	**Confirm** by another aminotransferase test; **if confirmed**, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, ▪ in patients >12 years, consider reintroduction of the treatment of 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days.
> 8 x ULN	**Stop** treatment permanently. There is no experience with reintroduction of bosentan in these circumstances.

Discontinue bosentan if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury, or increases in bilirubin of ≥2 x ULN.

Prescriber Steps in the Bosentan REMS

Prescribers must complete the following steps in the Bosentan REMS:

1. **READ the Prescribing Information for bosentan and this guide to understand the risks of bosentan and to learn about the Bosentan REMS**
   - You must understand the risks of bosentan and become familiar with the Bosentan REMS

2. **COMPLETE a *Prescriber Enrollment Form***
   - By signing the form, you attest to understanding the risks of bosentan and agree to comply with the requirements of the Bosentan REMS
   - You can complete the ***Prescriber Enrollment Form*** online or download paper copies from the ***Bosentan REMS Website*** at **www.BosentanREMSProgram.com** and fax the form to the Bosentan REMS at 1-800-730-8231

3. **DETERMINE the reproductive potential status for female patients**
   - You should identify female patients as one of the following categories on the ***Patient Enrollment Form***:
     - **Female of Reproductive Potential:**
       - Females of reproductive potential include females who have entered puberty and all females who have a uterus and have not passed through menopause
       - For the purposes of this REMS, puberty includes those females who are at least Tanner Stage 3 and have not yet had a menses (pre-menarchal)
     - **Female of Non-Reproductive Potential** (choose one of the options below)
       - Pre-pubertal female: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
       - Post-menopausal female: Females who have passed through menopause. Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy
       - Female with other medical reasons for permanent, irreversible infertility

4. **EDUCATE & COUNSEL all patients about the risks of bosentan**
   - For all patients, you must:
     - Counsel all patients on the risk of hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity and to contact the prescriber if they have any signs or symptoms of liver problems and REMS requirements including the need to complete liver testing and provide the ***Guide for Patients*** to each patient
     - Educate patients about the Bosentan REMS
   - For females of reproductive potential, you must:
     - Counsel patients about the risk of embryo-fetal toxicity, the need to complete monthly pregnancy tests, and the need to use reliable contraception during bosentan treatment, and for one month following treatment discontinuation

- Counsel the patient to immediately contact the prescriber if the patient misses a menstrual period, suspects that they are pregnant, had unprotected sex, or thinks that their birth control has failed
- Counsel the patient on the medical options in the event of unprotected sexual intercourse or known or suspected contraception failure
- Counsel patients who fail to comply with the REMS requirements

- For pre-pubertal females, you must:
  - Counsel the patient about the risk of embryo-fetal toxicity
  - Counsel the patient to immediately contact the prescriber when the patient begins to menstruate

5. ENROLL all patients in the Bosentan REMS by completing the *Patient Enrollment Form* with the patient

- Order and review a liver test for all patients, and a pregnancy test for females of reproductive potential
- Confirm the patient has agreed to comply with the REMS requirements and has signed the form where indicated
- Complete the form online at **www.BosentanREMSProgram.com** or fax the completed form to the Bosentan REMS at 1-800-730-8231
- Keep the original form with the patient's records and provide a completed copy of the form to the patient

6. REVIEW all required test results and monitor patients throughout treatment

- **For all patients:**
  - Order and review liver tests each month during treatment with bosentan
  - Confirm, when necessary, the completion of liver tests and counseling each month by one of the following methods:
    - Entering the testing and counseling information online at **www.BosentanREMSProgram.com**
    - Submitting a ***Testing and Patient Counseling Reporting Form*** by fax to the Bosentan REMS at 1-800-730-8231
    - Calling the Bosentan REMS at 1-866-359-2612
  - For changes in aminotransferase levels, adjust the monitoring and treatment with bosentan
  - Discontinue bosentan if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN
- **For all females of reproductive potential:**
  - Order and review pregnancy tests monthly during treatment with bosentan and for one month following treatment discontinuation
  - Prescribers may confirm the completion of pregnancy tests and counseling each month by one of the following methods:
    - Entering the testing and counseling information online at **www.BosentanREMSProgram.com**
    - Submitting a ***Testing and Patient Counseling Reporting Form*** by fax to the Bosentan REMS at 1-800-730-8231

    - Calling the Bosentan REMS at 1-866-359-2612
  - Monitor patient's reproductive status during treatment with bosentan and report any change or misclassification in reproductive potential status by submitting a ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** to the Bosentan REMS within 10 business days of becoming aware of the change
    - Prescribers can enter the information online at **www.BosentanREMSProgram.com** or fax the completed form to the Bosentan REMS at 1-800-730-8231

- **For females of non-reproductive potential:**
  - Monitor patient's reproductive status during treatment with bosentan and report any change or misclassification in reproductive potential status by submitting a ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** to the Bosentan REMS within 10 business days of becoming aware of the change
    - Prescribers can enter the information online at **www.BosentanREMSProgram.com** or fax the completed form to the Bosentan REMS at 1-800-730-8231
  - For each patient who is 8 years of age or older[1], verify at least annually and report the reproductive status by completing and submitting the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** to the Bosentan REMS

Prescriber Designees

Certified prescribers can add prescriber designees on the *Bosentan REMS Website*

The certified prescriber of record is responsible for compliance with the REMS requirements and ensuring the REMS requirements are being followed by the prescriber designee. The certified prescriber of record is responsible for monitoring, evaluating, and managing of each patient under their care.

- **The following activities must be performed by the certified prescriber and cannot be delegated:**
  - Completing and submitting a ***Prescriber Enrollment Form***
  - Completing and submitting a ***Patient Enrollment Form***
  - Submitting a change in reproductive potential status or verifying pre-pubertal status annually
  - Granting a Refill Dispense Exception
  - Adding other prescriber designees
- **A prescriber can delegate the following activities to a prescriber designee:**
  - Updating patient information with the Bosentan REMS after the patient has already been enrolled
  - Confirming completion of patient liver testing and, for females of reproductive potential, pregnancy testing
  - Confirming completion of patient counseling

7. NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity

8. REPORT pregnancies to the Bosentan REMS

[1] Clinical threshold for evaluating onset of puberty.

All Bosentan REMS forms can be completed online or downloaded from the website at **www.BosentanREMSProgram.com**. Hard copies can be faxed to the REMS at 1-800-730-8231. Other information about the Bosentan REMS can be found on the ***Bosentan REMS Website***. The Contact Center can be reached at 1-866-359-2612.

Important Information for Prescribers for Females of Reproductive Potential Taking Bosentan

- Educate and counsel females of reproductive potential about medical options in the event of unprotected sex or known or suspected contraceptive failure
- Remind the patient to report missing a menstrual period or any other reason for suspected pregnancy during treatment to you immediately
- If pregnancy is suspected for any reason, a pregnancy test must be performed
- The prescriber must notify the Bosentan REMS at 1-866-359-2612 of pregnancies

What is a Refill Dispense Exception?

The Bosentan REMS allows prescribers to apply clinical judgment and authorize continued dispensing of bosentan to enrolled patients when a patient's testing could not be confirmed in a given month or for extended travel outside of the United States. In order for a pharmacy to dispense to a patient, the prescriber must authorize a refill dispense exception.

A refill dispense exception allows a prescriber to authorize a patient to receive up to a 30-day supply of bosentan without a confirmed pregnancy and/or liver testing. The refill dispense exception also allows the prescriber to authorize up to a 90-day supply of bosentan for extended travel outside of the United States of more than 30 days.

In order for a patient to be eligible to receive a refill dispense exception due to testing not being confirmed in a given month:

- The patient must be enrolled in the Bosentan REMS
- The patient must have confirmed testing on file for the previous month
- The prescriber must attest that the benefits of receiving bosentan outweigh the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan

In order for a patient to be eligible to receive a refill dispense exception for extended travel outside of the United States:

- The patient must be enrolled in the Bosentan REMS
- The patient must have confirmed testing on file for the previous month
- The patient must be traveling outside of the United States for more than 30 days
- The prescriber must attest that the benefits of receiving bosentan outweigh the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan
- The prescriber must attest to continue to counsel the patient about the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan, the signs and symptoms of hepatotoxicity, and REMS requirements including the need to complete liver testing and, as appropriate, pregnancy testing monthly while traveling outside of the United States

  - Test confirmation is not required to be provided to the Bosentan REMS while the patient is traveling outside of the United States

Only certified prescribers can authorize a refill dispense exception by:

- Calling the Contact Center at 1-866-359-2612
- Documenting the refill dispense exception authorization through the ***Bosentan REMS Website***

Contraception for Females of Reproductive Potential

All females of reproductive potential must use reliable contraception during treatment with bosentan and for one month following treatment discontinuation. Patients should also have monthly contraceptive counseling with either the prescriber or another designated healthcare provider trained in contraceptive counseling. Please refer to the table below for a complete list of acceptable contraceptive methods. A similar table can be found in the ***Guide for Patients*** and should be used to discuss acceptable birth control options with patients. The patient should be instructed to select one of the options listed below.

Option 1	Option 2	Option 3	Option 4
One method from this list:	**One method from this list:**	**One method from this list:**	**One method from this list:**
Standard intrauterine device (Copper T 380A IUD)	Estrogen and progesterone oral contraceptives ("the pill")	Diaphragm with spermicide	Partner's vasectomy
Intrauterine system (LNg 20 IUS: progesterone IUS)	Estrogen and progesterone transdermal patch	Cervical cap with spermicide	**PLUS One method from this list:**
Tubal sterilization	Vaginal ring	**PLUS One method from this list:**	Male condom
	Progesterone injection	Male condom	Diaphragm with spermicide
	Progesterone implant		Cervical cap with spermicide
	PLUS One method from this list:		Estrogen and progesterone oral contraceptives ("the pill")
	Male condom		Estrogen and progesterone transdermal patch
	Diaphragm with spermicide		Vaginal ring
	Cervical cap with spermicide		Progesterone injection
			Progesterone implant

Bosentan
REMS Program

You can reach the Contact Center by calling toll free 1-866-359-2612. For more information about the Bosentan REMS, please visit **www.BosentanREMSProgram.com**.

Please see the Prescribing Information for bosentan, including complete Boxed Warning for hepatotoxicity and embryo-fetal toxicity, and the Medication Guide for each approved bosentan product, which can be found at **www.BosentanREMSProgram.com**.

BACKGROUND

The Bosentan REMS was approved by the Food and Drug Administration (FDA) for all bosentan products. In the Bosentan REMS:

Patients must be enrolled in the Bosentan REMS. Prescribers must complete the ***Patient Enrollment Form*** for each patient.

Prescribers must be certified in the Bosentan REMS.

Pharmacies must be certified in the Bosentan REMS.

Prescriptions require a Pre-Dispense Authorization (PDA) from the Bosentan REMS before a certified outpatient pharmacy can dispense bosentan. A PDA is verification sent to outpatient and chain pharmacies by the Bosentan REMS, authorizing the pharmacy to dispense bosentan to an eligible patient.

Certified inpatient pharmacies are not required to obtain a PDA from the Bosentan REMS, but must implement processes and procedures to confirm that the patient is eligible to receive bosentan.

STAKEHOLDER	BOSENTAN REMS REQUIREMENTS
OUTPATIENT PHARMACIES[i]	• **Designate an authorized representative to oversee the implementation of and compliance with the Bosentan REMS** **To become certified, the authorized representative must:** • Review the **Pharmacy Guide**. • Enroll in the Bosentan REMS by completing the **Outpatient Pharmacy Enrollment Form** and submitting it to the Bosentan REMS. • Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the **Pharmacy Guide**. **Before dispensing, the pharmacy must:** **For all patients:** • Obtain authorization to dispense each prescription by contacting the Bosentan REMS to verify: o the patient is enrolled, o the prescriber is certified, o the pharmacy is certified, o if counseling is complete, o liver testing is complete, o the reproductive status has not changed for female patients, and o the pregnancy test is completed for females of reproductive potential or the prescriber authorizes the refill. • Dispense no more than a 30 days' supply. **For patients without documented testing:** • Communicate with the patient or prescriber to confirm testing. • Document and submit the confirmation of testing using the Bosentan REMS Website or by calling the Contact Center. **For all patients without documented counseling on hepatotoxicity:** • Counsel the patient on the risk of hepatotoxicity. • Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center. **For females of reproductive potential and pre-pubertal females without documented counseling on embryo-fetal toxicity:** • Counsel the patient on the risk of embryo-fetal toxicity. • Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center. **At all times the pharmacy must:** • Report adverse events suggestive of hepatotoxicity to the Bosentan REMS. • Report pregnancies to the Bosentan REMS. • Not distribute, transfer, loan, or sell bosentan, except to certified dispensers. • Maintain records of o dispensing, o training, and o that all processes and procedures are in place and are being followed. • Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed. • Have the new authorized representative certify in the Bosentan REMS by completing the **Outpatient Pharmacy Enrollment Form** if the authorized representative changes.

Reference ID: 4976585

	Any pharmacist or pharmacy employee in a certified pharmacy may assume the role of pharmacy staff to conduct basic REMS functions by accessing the *Bosentan REMS Website* The authorized representative for the pharmacy is responsible for maintaining the list of staff associated with the pharmacy and ensuring the REMS requirements are being followed by the pharmacy staff
CHAIN PHARMACIES[ii]	• **Designate an authorized representative to oversee the implementation of and compliance with the Bosentan REMS** • **To become certified the authorized representative must:** 1. Complete and sign the ***Chain Pharmacy Headquarters Enrollment Form*** on behalf of the pharmacy, and submit the form to the Bosentan REMS 2. Comply with the requirements in the Outpatient Pharmacies section above 3. Once the ***Chain Pharmacy Headquarters Enrollment Form*** has been processed, the authorized representative will receive a pharmacy certification confirmation. Upon receipt, the chain pharmacy headquarters is certified and dispensing locations are now eligible to complete their training 4. Once each dispensing location is trained, the authorized representative must report confirmation of training to the Bosentan REMS online through **www.BosentanREMSProgram.com**, or by calling the Contact Center at 1-866-359-2612 to obtain instructions on providing a list of trained pharmacy locations. Once the Bosentan REMS confirms the required dispensing information, the dispensing location will be authorized to purchase, receive, and dispense bosentan **Any pharmacist or pharmacy employee in a certified pharmacy may assume the role of pharmacy staff to conduct basic REMS functions by accessing the *Bosentan REMS Website*** The authorized representative for the pharmacy is responsible for maintaining the list of staff associated with the pharmacy and ensuring the REMS requirements are being followed by the pharmacy staff
INPATIENT PHARMACIES[iii]	• **Designate an authorized representative to oversee the implementation of and compliance with the Bosentan REMS** • **To become certified the authorized representative must:** ◦ Review the **Pharmacy Guide**. ◦ Enroll in the Bosentan REMS by completing the **Inpatient Pharmacy Enrollment Form** and submitting it to the Bosentan REMS. ◦ Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the **Pharmacy Guide**. ◦ Establish processes and procedures to verify: ▪ the patient is enrolled or will be enrolled prior to discharge, ▪ the patient is under the care of a certified prescriber, ▪ counseling is complete, ▪ liver testing is complete, and ▪ pregnancy testing is complete (for females of reproductive potential). **Before dispensing, the pharmacy must:** ◦ Verify the patient: ▪ is enrolled or will be prior to discharge, ▪ is under the care of a certified prescriber, ▪ counseling is complete, ▪ completed liver testing, and ▪ completed pregnancy testing (for females of reproductive potential). **At all times, the pharmacy must:** ◦ Have the new authorized representative certify in the Bosentan REMS by completing the **Inpatient Pharmacy Enrollment Form** if the authorized representative changes. ◦ Report adverse events suggestive of hepatotoxicity to the Bosentan REMS. ◦ Report pregnancies to the Bosentan REMS. ◦ Not distribute, transfer, loan, or sell bosentan, except to certified dispensers. ◦ Maintain records of training. ◦ Maintain records that all processes and procedures are in place and are being followed. ◦ Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed. **At discharge, the pharmacy must:** ◦ Dispense no more than a 15 days' supply. **Any pharmacist or pharmacy employee in a certified pharmacy may assume the role of pharmacy staff to conduct basic REMS functions by accessing the *Bosentan REMS Website*** The authorized representative for the pharmacy is responsible for maintaining the list of staff associated with the pharmacy and ensuring the REMS requirements are being followed by the pharmacy staff

	The authorized representative for the pharmacy is responsible for maintaining the list of staff associated with the pharmacy and ensuring the REMS requirements are being followed by the pharmacy staff
PHARMACY STAFF	• Any pharmacist or pharmacy employee in a certified pharmacy may assume the role of pharmacy staff to conduct basic REMS functions by accessing the ***Bosentan REMS Website*** • Pharmacy staff in outpatient pharmacies can: 1. Request a PDA or reverse a PDA 2. Confirm completion of liver testing and pregnancy testing (if applicable) on the ***Bosentan REMS Website*** 3. Complete counseling and confirm completion on the ***Bosentan REMS Website*** • Pharmacy staff for inpatient pharmacies will be able to verify prescriber certification and patient enrollment
PRESCRIBERS	• **To become certified to prescribe bosentan, each prescriber must:** • Review the Prescribing Information and the **Prescriber Guide**. • Enroll in the Bosentan REMS by completing the **Prescriber Enrollment Form** and submitting it to the Bosentan REMS. **Before treatment initiation (first dose), each prescriber must:** **For all patients:** • Provide the patient a copy of the **Guide for Patients**. • Enroll the patient by completing and submitting the **Patient Enrollment Form** to the Bosentan REMS. Provide a completed copy to the patient. • Counsel the patient on the risk of hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity, to contact the prescriber if the patient has any signs or symptoms of liver problems, and program requirements including the need to complete liver testing using the **Guide for Patients**. • Assess the patient's liver function. Document and submit to the Bosentan REMS using the **Patient Enrollment Form**. **For all females**: • Assess the patient's reproductive status using the definitions in the **Prescriber Guide**. Document and submit to the Bosentan REMS using the **Patient Enrollment Form**. **For pre-pubertal females**: • Counsel the patient about the risk of embryo-fetal toxicity and the need to immediately contact the prescriber when the patient begins to menstruate using the **Guide for Patients**. **For females of reproductive potential:** • Counsel the patient about the risk of embryo-fetal toxicity, the need to use reliable contraception as defined in the **Prescriber Guide** during treatment and for one month following treatment discontinuation, the need to complete pregnancy testing, the need to contact the prescriber if pregnancy is suspected, and emergency contraception using the **Guide for Patients**. • Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results. Document and submit to the Bosentan REMS using the **Patient Enrollment Form**. **During treatment; monthly, each prescriber must:** **For all patients:** • Assess the patient's liver function and counsel the patient on the risk of hepatotoxicity. **For females of reproductive potential:** • Counsel the patient on the risk of embryo-fetal toxicity. • Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results. **During treatment; at least annually, each prescriber must:** **For pre-pubertal females age 8 years or older:** • Document reproductive status and submit to the Bosentan REMS using the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**. **After treatment discontinuation; for one month, each prescriber must:** **For females of reproductive potential**: • Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results. **At all times, each prescriber must:** • Report adverse events suggestive of hepatotoxicity to the Bosentan REMS. • Report pregnancies to the Bosentan REMS. **For pre-pubertal females:** • Assess the patient's reproductive status. **At all times, within 10 business days, each prescriber must:** • Report a change or misclassification in reproductive status to the Bosentan REMS using the **Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form**.

	Certified prescribers can add prescriber designees on the *Bosentan REMS Website* The certified prescriber of record is responsible for compliance with the REMS requirements and ensuring the REMS requirements are being followed by the prescriber designee. The certified prescriber of record is responsible for monitoring, evaluation, and management of each patient under their care. The following activities must be performed by the certified prescriber and cannot be delegated: 1. Completing and submitting a ***Prescriber Enrollment Form*** 2. Completing and submitting a ***Patient Enrollment Form*** 3. Submitting a change in reproductive potential status or verifying pre-pubertal status annually 4. Granting a Refill Dispense Exception • Adding other prescriber designees
PRESCRIBER DESIGNEES	A prescriber can delegate the following activities to a prescriber designee: 1. Updating patient information with the Bosentan REMS after the patient has already been enrolled 2. Confirming completion of patient liver testing and, for females of reproductive potential, pregnancy testing 3. Confirming completion of patient counseling
PATIENTS/PARENTS/LEGAL GUARDIANS	• **Each patient and/or parent/legal guardian must complete and sign the *Patient Enrollment Form* with the prescriber to indicate that:** **FEMALES OF REPRODUCTIVE POTENTIAL** **Before treatment, I must:** • Review the **Guide for Patients**. • Get a liver test and a pregnancy test. • Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS. • Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, the need to complete liver testing, the risk of serious birth defects, the need to use reliable contraception during treatment and for one month following treatment discontinuation, the need to complete pregnancy testing, the need to contact the prescriber if I suspect I am pregnant, and emergency contraception using the **Guide for Patients**. **During treatment, before each prescription, I must:** • Get a liver test and a pregnancy test. • Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of pregnancy testing and liver testing. • Receive counseling from the prescriber or pharmacy on the risks of liver problems and serious birth defects associated with bosentan treatment. **During treatment and after treatment discontinuation for one month, I must:** • Adhere to the safe use condition: Use reliable contraception as described in the **Guide for Patients**. **After treatment discontinuation for one month, I must:** • Get a pregnancy test. **At all times, I must:** • Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients**. • Inform the prescriber immediately if I suspect I may be pregnant. **PRE-PUBERTAL FEMALES** **Before treatment, I must:** • Review the **Guide for Patients**. • Get a liver test. • Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS. • Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, the need to complete liver testing, the risk of serious birth defects, and the need to contact the prescriber when I begin to menstruate using the **Guide for Patients**. **During treatment, before each prescription, I must:** • Get a liver test. • Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of liver testing.

- Receive counseling from the prescriber or pharmacy on the risks of liver problems and serious birth defects associated with bosentan treatment.

At all times, I must:

- If over the age of 8: Be monitored for a change in reproductive status.
- Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients**.
- Inform the prescriber if I have a change in reproductive status.

POST-MENOPAUSAL FEMALES OR FEMALES WITH OTHER MEDICAL REASONS FOR PERMANENT, IRREVERSIBLE INFERTILITY

Before treatment, I must:

- Review the **Guide for Patients**.
- Get a liver test.
- Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS.
- Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, and the need to complete liver testing using the **Guide for Patients**.

During treatment, before each prescription, I must:

- Get a liver test.
- Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of liver testing.
- Receive counseling from the prescriber or pharmacy on the risk of liver problems associated with bosentan treatment.

At all times, I must:

- Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients**.
- Inform the prescriber if I have a change in reproductive status.

MALES

Before treatment, I must:

- Review the **Guide for Patients**.
- Get a liver test.
- Enroll in the Bosentan REMS by completing the **Patient Enrollment Form** with the prescriber. Enrollment information will be provided to the Bosentan REMS.
- Receive counseling from the prescriber on the risk of liver problems, the signs and symptoms of liver problems, the need to contact the prescriber if I have any signs or symptoms of liver problems, and the need to complete liver testing using the **Guide for Patients**.

During treatment, before each prescription, I must:

- Get a liver test.
- Adhere to the safe use condition: Communicate with the Bosentan REMS or pharmacy to confirm completion of liver testing.
- Receive counseling from the prescriber or pharmacy on the risk of liver problems associated with bosentan treatment.

At all times, I must:

- Inform the prescriber if I have any signs or symptoms of liver problems as described in the **Guide for Patients**.

BOSENTAN REMS Pre-Dispense Authorization (PDA) SCENARIOS FOR PHARMACIES	PDA ISSUED*
Pharmacy is certified, prescriber is certified, patient is enrolled, patient has completed the required test(s), and current appropriate counseling is confirmed.	✓
Patient liver test is not on file, but later confirmed to have taken place If patient does not have a current completed liver test confirmed with the Bosentan REMS, a PDA will not be issued. The pharmacy can confirm with the patient or the prescriber that a liver test was completed and enter this confirmation on the ***Bosentan REMS Website***.	✓
Pregnancy test for a female of reproductive potential is not on file, but later confirmed to have taken place If patient does not have a current completed pregnancy test confirmed with the Bosentan REMS, a PDA will not be issued. The pharmacy can confirm with the patient or the prescriber that a pregnancy test was completed and enter this confirmation on the ***Bosentan REMS Website***.	✓
Counseling is not on file, but later confirmed to have taken place If all safe use conditions are met but the patient does not have current appropriate counseling confirmed with the Bosentan REMS, a PDA will be issued by the Bosentan REMS, with a message instructing the pharmacist to complete counseling prior to dispensing bosentan. The pharmacy can view the counseling guidelines and confirm completion of counseling on the ***Bosentan REMS Website***.	✓
Pharmacy is not certified If a pharmacy is not certified in the Bosentan REMS, a PDA will not be issued.	✗
Prescriber is not certified If a prescriber is not certified in the Bosentan REMS, a PDA will not be issued.	✗
Patient is not enrolled If a patient is not enrolled in the Bosentan REMS, a PDA will not be issued.	✗
Patient liver test is not confirmed If a patient does not have a current completed liver test confirmed with the Bosentan REMS, a PDA will not be issued.	✗
Pregnancy test for females of reproductive potential is not confirmed If a female of reproductive potential does not have a current pregnancy test confirmed with the Bosentan REMS, a PDA will not be issued.	✗

*A green checkmark indicates approval to dispense bosentan to the patient. A red 'X" indicates safe use conditions have not been met and bosentan should not be dispensed to the patient.

[i] For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.

[ii] For the purposes of this REMS, chain pharmacies are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.

[iii] For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

Reference ID: 4976585

Bosentan

REMS Program

Pharmacy Guide

The Bosentan **R**isk **E**valuation and **M**itigation **S**trategy (REMS) is a single shared system for brand and generic bosentan medication for the treatment of pulmonary arterial hypertension (PAH). Due to the risks of hepatotoxicity and embryo-fetal toxicity, bosentan is only available through the Bosentan REMS.

This guide contains important information for pharmacies about the risks of bosentan, including boxed warnings for hepatotoxicity and embryo-fetal toxicity, and includes:

- Authorized Representatives and Pharmacy Certification Information
- Pre-Dispense Authorization (PDA) for Dispensing Bosentan
- Outpatient and Chain Pharmacies' Role in the Bosentan REMS: Step by Step
- Inpatient Pharmacies' Role in the Bosentan REMS: Step by Step
- Counseling and Contraception for Females of Reproductive Potential

Table of Contents

About Bosentan

Tracleer® (bosentan) is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).
- in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

Bosentan is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).

Risk of Hepatotoxicity

Bosentan may cause liver problems. Liver monitoring is essential prior to initiation of treatment and monthly thereafter. It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.

Changes in aminotransferases may occur early or late in treatment. There have been rare postmarketing reports of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring; the contribution of bosentan could not be excluded.

Elevations in aminotransferases require close attention. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. Use of bosentan should generally be avoided in patients with elevated aminotransferases (>3 × ULN) **at baseline** because monitoring for hepatotoxicity may be more difficult.

Risk of Embryo-fetal Toxicity

Bosentan is contraindicated in females who are or may become pregnant and may cause fetal harm when administered to a pregnant woman. Animal studies have shown that bosentan is likely to cause major birth defects when administered during pregnancy. If bosentan is used during pregnancy, apprise the patient of the potential hazard to a fetus. To prevent pregnancy, females of reproductive potential must use reliable contraception prior to beginning treatment with bosentan, during treatment and for one month following treatment discontinuation. Patients must not become pregnant while taking bosentan.

Bosentan REMS Overview

Due to the risks of hepatotoxicity and embryo-fetal toxicity, bosentan is only available through a single shared system required and approved by the Food and Drug Administration (FDA), called the Bosentan REMS. The Bosentan REMS is a single shared system including all brand and generic bosentan products.

The goal of the Bosentan REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan by:

- Ensuring prescribers are educated on the following:
  - the risks of hepatotoxicity and embryo-fetal toxicity
- Ensuring prescribers are educated on and adhere to the following:
  - counseling patients about these risks and the need for monthly monitoring
  - enrolling patients in the Bosentan REMS
  - monitoring patients at baseline and monthly
- Ensuring that pharmacies are educated on the following:
  - the risks of hepatotoxicity and embryo-fetal toxicity
- Ensuring that pharmacies are educated on and adhere to the following:
  - confirming that the appropriate patient monitoring and counseling has occurred before dispensing bosentan
- Ensuring that patients are informed about:
  - the risks of hepatotoxicity and embryo-fetal toxicity
  - appropriate baseline and monthly patient monitoring
  - appropriate contraception

Bosentan REMS Pharmacy Types and Definitions

All outpatient, chain, and inpatient pharmacies must certify in the Bosentan REMS to purchase and dispense bosentan. Pharmacies participating in the Bosentan REMS must determine their pharmacy type based on the definitions below:

Pharmacy Type	Definition
Outpatient Pharmacy	For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.
Chain Pharmacy	For the purposes of this REMS, chain pharmacies are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.
Inpatient Pharmacy	For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

Authorized Representatives and Pharmacy Certification

To become certified, pharmacies must designate an authorized representative to complete enrollment.

An authorized representative for a pharmacy may be, but is not limited to:

- Pharmacy Manager
- Staff Pharmacist
- Director of Pharmacy Services
- Corporate Executive overseeing Pharmacy Service

In general, an authorized representative for a pharmacy:

- Trains all relevant staff involved in the dispensing of bosentan on the Bosentan REMS
- Coordinates the activities required for the pharmacy and/or pharmacy staff in the Bosentan REMS
- Maintains records of training
- Maintains records that all processes and procedures are in place and are being followed
- Complies with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed

Specific duties of an outpatient pharmacy authorized representative are referenced on page 10

Specific duties of a chain pharmacy authorized representative are referenced on page 12

Specific duties of an inpatient pharmacy authorized representative are referenced on page 14

Note: New authorized representatives must certify in the Bosentan REMS if the authorized representative changes. All pharmacies will be contacted to verify the name and contact information of the pharmacy's authorized representative every 2 years.

Pre-Dispense Authorization (PDA) for Dispensing Bosentan for Outpatient Pharmacies

A PDA is verification by the Bosentan REMS authorizing the pharmacy to dispense bosentan to an eligible patient.

Chain and outpatient pharmacies must obtain a PDA from the Bosentan REMS for each dispense of bosentan that verifies the following safe use conditions are met for the patient:

- Patient is enrolled in the Bosentan REMS
- Prescriber is certified in the Bosentan REMS
- Pharmacy is certified in the Bosentan REMS
- Current completed liver test for the patient is confirmed
  - If liver testing is not confirmed, the pharmacy can confirm with the patient or prescriber that the testing has been completed and enter this confirmation on the ***Bosentan REMS Website*** or call the Contact Center
- If the patient is a female of reproductive potential, a current completed pregnancy test for the patient is confirmed
  - If pregnancy testing is not confirmed, the pharmacy can confirm with the patient or prescriber that testing has been completed and enter this confirmation on the ***Bosentan REMS Website*** or call the Contact Center
- Current hepatotoxicity counseling for the patient is confirmed
  - If counseling is not confirmed, the pharmacy can complete the counseling and confirm completion of counseling on the ***Bosentan REMS Website*** or by calling the Contact Center
- Current embryo-fetal toxicity counseling for each female of reproductive potential and pre-pubertal female is confirmed
  - If counseling is not confirmed, the pharmacy can complete the counseling and confirm completion of counseling on the ***Bosentan REMS Website*** or by calling the Contact Center

To verify the safe use conditions in the Bosentan REMS, chain and outpatient pharmacies must submit the following prescription information, at a minimum:

- Patient First Name
- Patient Last Name
- Patient Date of Birth
- Patient Zip Code
- Prescriber Identifier (e.g., NPI)
- Date of Fill
- Days' Supply
- Quantity
- Product / NDC

Once a PDA is obtained, the chain or outpatient pharmacy can dispense bosentan to the patient.

A PDA must be reversed if bosentan is not dispensed to the patient.
Your pharmacy must reverse the PDA by calling the Contact Center or accessing the ***Bosentan REMS Website***.

A prescriber may authorize a refill dispense exception.
A refill dispense exception allows a prescriber to authorize a patient to receive up to a 30 days' supply of bosentan without confirmed pregnancy and/or liver testing, or up to a 90 days' supply of bosentan for extended travel outside of the United States of more than 30 days.

Refill dispense exception reasons are below:

- **Required Testing Not Confirmed – Benefit Outweighs the Risk:** The prescriber attests that testing has not been confirmed within the last month and that the benefits of receiving bosentan outweigh the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan.
- **Travel Outside of the United States for more than 30 Days:** The prescriber attests to continue to counsel the patient about the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan, the signs and symptoms of hepatotoxicity, and REMS requirements including the need to complete liver testing and, as appropriate, pregnancy testing monthly while traveling outside of the United States.

If upon patient consult with the prescriber, the prescriber chooses to continue the patient on bosentan, a refill dispense exception must be provided to the Bosentan REMS from the prescriber.

After the prescriber provides the refill dispense exception, the Bosentan REMS will issue a PDA which allows your outpatient pharmacy to dispense bosentan to the patient.

Steps for Outpatient Pharmacies

The authorized representative for each outpatient pharmacy must complete the following steps in the Bosentan REMS:

1. **READ this guide to understand the risks of bosentan and to learn about the Bosentan REMS**
   - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS, prior to certifying their pharmacy
2. **ENROLL the pharmacy by completing the *Outpatient Pharmacy Enrollment Form***
   - By signing the form, the authorized representative attests to understanding the risks of bosentan and agrees to comply with the Bosentan REMS as described on the ***Outpatient Pharmacy Enrollment Form***
   - The authorized representative can complete the enrollment form online or download paper copies from the ***Bosentan REMS Website*** at **www.BosentanREMSProgram.com** and fax the form to the Bosentan REMS at 1-800-730-8231
3. **TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS requirements**
   - Prior to dispensing bosentan, the authorized representative must ensure that all pharmacy staff who participate in dispensing bosentan are educated on the risks associated with bosentan and the requirements of the Bosentan REMS, including obtaining a Pre-Dispense Authorization (PDA) verifying that safe use conditions are met for the patient prior to dispensing bosentan, as defined on the ***Outpatient Pharmacy Enrollment Form***
   - Any pharmacy employee may assume the role of pharmacy staff by associating with a certified outpatient pharmacy on the ***Bosentan REMS Website***
4. **DOCUMENT all staff training**
   - Certified pharmacies are subject to audit by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed
5. **VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan**
   - Outpatient pharmacies must dispense bosentan to patients only after obtaining a PDA by calling the Contact Center or accessing the ***Bosentan REMS Website***
     - If a PDA is not issued, prior to dispensing bosentan, the outpatient pharmacy may perform the corresponding activity to address the reasons that a PDA was not issued:
       - Contact the prescriber or the Bosentan REMS to indicate the prescriber is not certified and must become certified in the Bosentan REMS before bosentan can be dispensed
       - Contact the prescriber or the Bosentan REMS to notify the prescriber that the patient is not enrolled and must be enrolled in the Bosentan REMS before bosentan can be dispensed
       - If a PDA is not issued because required testing is not confirmed, the outpatient pharmacy can confirm with the patient or prescriber that the testing has been completed and enter this confirmation on the ***Bosentan REMS Website*** or call the Contact Center

- If counseling is not confirmed in the Bosentan REMS, a PDA will be issued if all other safe use conditions are met. The outpatient pharmacy must complete counseling prior to dispensing bosentan and can confirm completion on the ***Bosentan REMS Website*** or by calling the Contact Center

6. **DISPENSE up to a 30 days' supply**
   - Up to a 90 days' supply may be dispensed with a refill dispense exception authorized by the prescriber for extended travel outside of the United States of more than 30 days.
7. **DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS**
8. **NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity**
9. **REPORT pregnancies to the Bosentan REMS**
10. **HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY in the Bosentan REMS if the authorized representative changes**

All Bosentan REMS forms can be completed online or downloaded from the website at **www.BosentanREMSProgram.com**. Hard copies can be faxed to the REMS at 1-800-730-8231. Other information about the Bosentan REMS can be found on the ***Bosentan REMS Website***. The Contact Center can be reached at 1-866-359-2612.

Steps for Chain Pharmacies

The authorized representative for the chain pharmacy must complete the following steps in the Bosentan REMS:

1. **READ this guide to understand the risks of bosentan and to learn about the Bosentan REMS**
   - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS, prior to certifying their pharmacy
2. **ENROLL the chain pharmacy by completing the *Chain Pharmacy Headquarters Enrollment Form***
   - By signing the form, the authorized representative attests to understanding the risks of bosentan and agrees to comply with the Bosentan REMS as described in the ***Chain Pharmacy Headquarters Enrollment Form***
   - The authorized representative can complete the enrollment form online or download paper copies from the ***Bosentan REMS Website*** at **www.BosentanREMSProgram.com** and fax the form to the Bosentan REMS at 1-800-730-8231
3. **TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS requirements**
   - Prior to dispensing bosentan, the authorized representative must ensure that all pharmacy staff who participate in dispensing bosentan are educated on the risks associated with bosentan and the requirements of the Bosentan REMS, including obtaining a Pre-Dispense Authorization (PDA) verifying that safe use conditions are met for the patient prior to dispensing bosentan, as defined on the ***Chain Pharmacy Headquarters Enrollment Form***
   - Any pharmacy employee may assume the role of pharmacy staff by associating with a certified chain pharmacy on the ***Bosentan REMS Website***
4. **DOCUMENT all staff training**
   - Once each dispensing location is trained, it is the authorized representative's responsibility to report confirmation of training to the Bosentan REMS online through the ***Bosentan REMS Website***, or by calling the Contact Center at 1-866-359-2612 to obtain instructions on providing a list of trained pharmacy locations. Once the Bosentan REMS confirms the required dispensing information, the dispensing location will be authorized to purchase, receive, and dispense bosentan
   - Certified pharmacies are subject to audit by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed
5. **VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan**
   - Chain pharmacies must dispense bosentan to patients only after obtaining a PDA by calling the Contact Center or accessing the ***Bosentan REMS Website***
   - If a PDA is not issued, prior to dispensing bosentan, the pharmacy may perform the corresponding activity to address the reasons that a PDA was not issued:
     - Contact the prescriber or the Bosentan REMS to indicate that the prescriber is not certified and must become certified in the Bosentan REMS before bosentan can be dispensed

- Contact the prescriber or the Bosentan REMS to notify the prescriber that the patient is not enrolled and must be enrolled in the Bosentan REMS before bosentan can be dispensed
- If a PDA is not issued because required testing is not confirmed, the pharmacy can confirm with the patient or prescriber that the testing has been completed and enter this confirmation on the ***Bosentan REMS Website*** or call the Contact Center
- If counseling is not confirmed in the Bosentan REMS, a PDA will be issued if all other safe use conditions are met. The pharmacy must complete counseling prior to dispensing bosentan and can confirm completion on the ***Bosentan REMS Website*** or by calling the Contact Center

6. **DISPENSE up to a 30 days' supply**
   - Up to a 90 days' supply may be dispensed with a refill dispense exception authorized by the prescriber for extended travel outside of the United States of more than 30 days.
7. **DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS**
8. **NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity**
9. **REPORT pregnancies to the Bosentan REMS**
10. **HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY in the Bosentan REMS if the authorized representative changes**

All Bosentan REMS forms can be completed online or downloaded from the website at **www.BosentanREMSProgram.com**. Hard copies can be faxed to the REMS at 1-800-730-8231. Other information about the Bosentan REMS can be found on the ***Bosentan REMS Website***. The Contact Center can be reached at 1-866-359-2612.

Steps for Inpatient Pharmacies

The authorized representative for each inpatient pharmacy must complete the following steps in the Bosentan REMS:

1. **READ this guide to understand the risks of bosentan and to learn about the Bosentan REMS**
   - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS, prior to certifying their pharmacy
2. **ENROLL the pharmacy by completing the *Inpatient Pharmacy Enrollment Form***
   - By signing the form, the authorized representative attests to understanding the risks of bosentan and agrees to comply with the Bosentan REMS as described on the ***Inpatient Pharmacy Enrollment Form***
   - The authorized representative can complete the enrollment form online or download paper copies from the ***Bosentan REMS Website*** at **www.BosentanREMSProgram.com** and fax the form to the Bosentan REMS at 1-800-730-8231
3. **TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS requirements**
   - Prior to dispensing bosentan, the authorized representative must ensure that all staff are appropriately trained on the Bosentan REMS procedures and materials as defined on the ***Inpatient Pharmacy Enrollment Form***
   - Any pharmacy employee may assume the role of pharmacy staff by associating with a certified inpatient pharmacy on the ***Bosentan REMS Website*** to verify safe use conditions for each patient prior to dispensing bosentan
4. **DOCUMENT all staff training**
   - Certified pharmacies are subject to audit by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed
5. **VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan**
   - Dispense bosentan to patients only after calling the Contact Center, accessing the ***Bosentan REMS Website***, or accessing the patient's medical record to:
     - Verify the patient is under the supervision of a prescriber who is certified
     - Verify the patient is enrolled or will be enrolled prior to discharge
     - Verify counseling is complete
     - Verify liver testing and pregnancy testing (for females of reproductive potential) is complete
6. **DISPENSE no more than a 15 days' supply of bosentan at discharge**
7. **DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS**
8. **NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity**
9. **REPORT pregnancies to the Bosentan REMS**
10. **HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY in the Bosentan REMS if the authorized representative changes**

All Bosentan REMS forms can be completed online or downloaded from the website at **www.BosentanREMSProgram.com**. Hard copies can be faxed to the REMS at 1-800-730-8231. Other information about the Bosentan REMS can be found on the ***Bosentan REMS Website***. The Contact Center can be reached at 1-866-359-2612.

Counseling and Contraception

All females of reproductive potential must use reliable contraception during treatment with bosentan and for one month following treatment discontinuation. Patients should also have monthly contraceptive counseling with either the prescriber or another designated healthcare provider trained in contraceptive counseling. Please refer to the table below for a complete list of acceptable contraceptive methods. A similar table can be found in the ***Guide for Patients*** and should be used to discuss acceptable birth control options with patients. The patient should be instructed to select one of the options listed below.

Option 1	Option 2	Option 3	Option 4
One method from this list:	**One method from this list:**	**One method from this list:**	**One method from this list:**
Standard intrauterine device (Copper T 380A IUD)	Estrogen and progesterone oral contraceptives ("the pill")	Diaphragm with spermicide	Partner's vasectomy
Intrauterine system (LNg 20 IUS: progesterone IUS)	Estrogen and progesterone transdermal patch	Cervical cap with spermicide	**PLUS One Method from this list:**
Tubal sterilization	Vaginal ring	**PLUS One Method from this list:**	Male condom
	Progesterone injection	Male condom	Diaphragm with spermicide
	Progesterone implant		Cervical cap with spermicide
	PLUS One Method from this list:		Estrogen and progesterone oral contraceptives ("the pill")
	Male condom		Estrogen and progesterone transdermal patch
	Diaphragm with spermicide		Vaginal ring
	Cervical cap with spermicide		Progesterone injection
			Progesterone implant

Definitions of Reproductive Potential Status

- **Females of Reproductive Potential**
  - Females of reproductive potential include females who have entered puberty and all females who have a uterus and have not passed through menopause
  - For the purposes of this REMS, puberty includes those females who are at least Tanner Stage 3 and have not yet had a menses (pre-menarchal)
- **Females of Non-Reproductive Potential**
  - **Pre-pubertal Females:** Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
  - **Post-menopausal Females:** Females who have passed through menopause. Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy
  - **Females with other medical reasons for permanent, irreversible infertility**

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You can reach the Contact Center by calling toll free 1-866-359-2612. For more information about the Bosentan REMS, please visit **www.BosentanREMSProgram.com**.

Please see the Prescribing Information for bosentan, including complete Boxed Warning for hepatotoxicity and embryo-fetal toxicity, and Medication Guides for each approved bosentan product, which can be found at **www.BosentanREMSProgram.com**.

Bosentan

REMS Program

Guide for Patients

Information to help you during your treatment with bosentan

Table of Contents

What is bosentan?

Bosentan is a prescription medicine used to treat certain types of pulmonary arterial hypertension (PAH), which is high blood pressure in the vessels of the lungs.

Bosentan can improve your ability to exercise and can slow the worsening of your physical condition and symptoms. Bosentan lowers high blood pressure in your lungs and lets your heart pump more efficiently.

What are the serious risks of bosentan?

Bosentan can cause **liver problems** and, if taken during pregnancy, can cause **serious birth defects.**

All patients – liver function must be monitored:

- Before you start taking bosentan,
- Every month while taking bosentan, and
- Any time your prescriber orders testing

Female patients – pregnancy must be avoided:

- Before you start taking bosentan,
- While taking bosentan, and
- For one month after you end bosentan treatment

What is the Bosentan Risk Evaluation and Mitigation Strategy (REMS)?

The Bosentan Risk Evaluation and Mitigation Strategy (REMS) tells patients and healthcare providers about the risks of liver problems and serious birth defects when taking bosentan. This REMS is required by the Food and Drug Administration (FDA). All patients must enroll in the Bosentan REMS to receive bosentan.

Bosentan REMS Requirements

- Be counseled on the requirements of the Bosentan REMS and the risk of liver problems
- Participate in the Bosentan REMS for as long as you are taking the medication, and for females of reproductive potential, for one month after ending bosentan treatment
- Get liver tests your prescriber orders for you before beginning treatment and monthly thereafter until ending bosentan treatment. Your prescriber will monitor your liver and may adjust or stop your treatment if there are signs of liver problems
- Tell your prescriber if you have had liver problems, including liver problems while on other medicines
- Be contacted by the Bosentan REMS or the pharmacy before receiving bosentan to provide confirmation that a current liver test was completed and you were counseled on the risks of bosentan and your requirements in the Bosentan REMS

Females who can get pregnant have additional requirements in the REMS

You are considered a female who can get pregnant if you:

- Have entered puberty, even if you have not started your menstrual period, and
- Have a uterus, and

Have not gone through menopause (have not had a menstrual period for at least 12 months for natural reasons, or have had your ovaries removed)

- Be counseled on the requirements of the Bosentan REMS and the risk of serious birth defects
- Be counseled before your first prescription and each month thereafter on the need to use reliable birth control during bosentan treatment, and for one month after ending bosentan treatment
- Complete a pregnancy test before beginning treatment with bosentan, monthly during bosentan treatment, and one month after ending bosentan treatment
- Be contacted by the Bosentan REMS or the pharmacy before receiving bosentan to provide confirmation that a pregnancy test was completed before beginning treatment, monthly during treatment, and one month after ending bosentan treatment
- Notify your prescriber immediately if you:
  - Had unprotected sex
  - Think that your birth control failed
  - Missed a menstrual period
  - Think you are pregnant
- Be contacted by a Bosentan REMS representative if you become pregnant while on bosentan or within one month after ending bosentan treatment
- A pre-pubertal female must immediately contact their prescriber when the patient begins to menstruate

Birth Control Options

Your healthcare provider will talk with you about your birth control options before you start bosentan. Ask your healthcare provider if you have any questions. Tell your healthcare provider if you want to change your birth control.

You must choose one of the four options listed below. More than one birth control method might be needed every time you have sex.

Acceptable birth control options

Option 1	or	Option 2	or	Option 3	or	Option 4
One method from this list:		**One method from this list:**		**One method from this list:**		**One method from this list:**
Standard intrauterine device (Copper T 380A IUD)		Estrogen and progesterone oral contraceptives ("the pill")		Diaphragm with spermicide		Partner's vasectomy
Intrauterine system (LNg 20 IUS: progesterone IUS)		Estrogen and progesterone transdermal patch		Cervical cap with spermicide		**PLUS One Method from this list:**
Tubal sterilization		Vaginal ring		**PLUS One Method from this list:**		Male condom
		Progesterone injection		Male condom		Diaphragm with spermicide
		Progesterone implant				Cervical cap with spermicide
		PLUS One Method from this list:				Estrogen and progesterone oral contraceptives ("the pill")
		Male condom				Estrogen and progesterone transdermal patch
		Diaphragm with spermicide				Vaginal ring
		Cervical cap with spermicide				Progesterone injection
						Progesterone implant

Steps to treatment with bosentan

BEFORE YOU START TREATMENT: All Patients

- ❒ Understand the risks of liver problems and birth defects (for females) while taking bosentan
- ❒ Tell your prescriber if you have had liver problems, including liver problems while taking other medicines
- ❒ Get your liver test
- ❒ Get your pregnancy test (for females who can get pregnant)
- ❒ Enroll in the Bosentan REMS. Complete and sign the ***Patient Enrollment Form*** with your prescriber. Your prescriber will fill out most of the enrollment form for you. You must read and agree to the requirements, then sign to show you understand and will follow the rules of the program. A parent/legal guardian may sign the form for you

EVERY MONTH: All Patients

- ❒ Read the Medication Guide that comes with every prescription. Important information may have been added or changed
- ❒ Get the monthly liver tests ordered by your prescriber
- ❒ Fill your prescription at a certified pharmacy. A certified pharmacy is a pharmacy that is authorized by the Bosentan REMS to provide bosentan to you. For a list of certified pharmacies, please call the Bosentan REMS at 1-866-359-2612 or visit **www.BosentanREMSProgram.com**
- ❒ The Bosentan REMS or the pharmacy will call you every month to ask if you had your liver tests and were counseled on the risk of liver problems before you can receive your bosentan. **If your healthcare provider has already notified the Bosentan REMS that you have completed your testing and counseling, you will not receive a phone call from the Bosentan REMS that month.** The refill may not be ready on time if you have not had your liver tests and counseling
- ❒ Tell your prescriber right away if you have any of these symptoms of liver problems while taking bosentan: nausea, vomiting, fever, unusual tiredness, stomach area (abdominal) pain, or yellowing of the skin or the whites of your eyes (jaundice)

EVERY MONTH: Female Patients Who Can Get Pregnant

- ❒ Use the reliable birth control method(s) agreed upon with your healthcare provider during treatment
- ❒ Get the monthly pregnancy test ordered by your prescriber
- ❒ The Bosentan REMS or the pharmacy will call you every month to ask if you had a pregnancy test and were counseled on the risk of birth defects before you can receive your bosentan. **If your healthcare provider has already notified the Bosentan REMS that you have completed your testing and counseling, you will not receive a phone call from the Bosentan REMS that month.** The refill may not be ready on time if you have not had your pregnancy test and counseling
- ❒ Do not get pregnant. Tell your prescriber right away if you: Had unprotected sex, think that your birth control failed, missed a menstrual period, think you are pregnant

ONE MONTH AFTER ENDING BOSENTAN TREATMENT: Female Patients Who Can Get Pregnant

- ❒ Use the reliable birth control method(s) agreed upon with your healthcare provider for one month after ending bosentan treatment
- ❒ Get the final pregnancy test ordered by your prescriber
- ❒ Do not get pregnant. Tell your prescriber right away if you: Had unprotected sex, think that your birth control failed, missed a menstrual period, think you are pregnant

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You can reach the Bosentan REMS by calling toll free at 1-866-359-2612.

For more information about the Bosentan REMS, please visit **www.BosentanREMSProgram.com**.

Bosentan
REMS Program

Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

NOTE: THIS FORM SHOULD NOT BE USED TOGETHER WITH THE *PATIENT ENROLLMENT FORM*.
USE THIS FORM ONLY TO REPORT A CHANGE IN REPRODUCTIVE POTENTIAL STATUS OR FOR PRE-PUBERTAL ANNUAL VERIFICATION.

Fax this form to the Bosentan REMS at 1-800-730-8231 or for immediate reporting, please go to www.BosentanREMSProgram.com.

Instructions

The patient's prescriber must use this form to:

1. Report a change or misclassification in reproductive potential status of any female patient within 10 business days of becoming aware of the change
2. Complete the annual verification of the reproductive potential status for patients age 8 years and older

If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit **www.BosentanREMSProgram.com**, or call the Bosentan REMS at 1-866-359-2612.

Patient Information (All fields required unless otherwise indicated)

First Name: MI (optional): Last Name: Phone:

Date of Birth (MM/DD/YYYY): Email (optional):

Address: City:

State: Zip Code:

Prescriber Information (All fields required unless otherwise indicated)

First Name: MI (optional): Last Name:

NPI#:

Phone: Fax: Email:

Definitions of Reproductive Potential Status

Females of Reproductive Potential

- Females of reproductive potential include females who have entered puberty and all females who have a uterus and have not passed through menopause (as defined below)
- For the purposes of this REMS, puberty includes those females who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non-Reproductive Potential

- Pre-pubertal females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-menopausal females: Females who have passed through menopause. Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical from bilateral oophorectomy
- Females with other medical reasons for permanent, irreversible infertility

Select (by checking the appropriate box) the most appropriate reason for submitting this form

Patient has had a change in reproductive status

Based on definitions of reproductive potential status, patient is (choose one):

- ❒ Female of reproductive potential
- ❒ Female of non-reproductive potential – Patient is pre-pubertal
- ❒ Female of non-reproductive potential – Patient is post-menopausal
- ❒ Female of non-reproductive potential – Other medical reasons for permanent, irreversible infertility

Reason for change in classification (choose one):

- ❒ Physiological transition
- ❒ Medical/Surgical (please specify):_____
- ❒ Other (please specify):_____

Annual verification of pre-pubertal status

- ❒ Patient remains a pre-pubertal female age 8 years or older

Prescriber Signature

By signing below, I attest that the patient's reproductive status as noted above is accurate, and that I will comply with the REMS requirements for my patient's reproductive potential status as defined in the Definitions section above and in the ***Prescriber Guide.***

Prescriber Signature **Date**

Reference ID: 4976585

Bosentan
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Testing and Patient Counseling Reporting Form

Phone: 1-866-359-2612
Fax: 1-800-730-8231

Instructions for Prescribers

This form may be used every month to confirm the completion of both liver and pregnancy tests on a single form. Completion of required tests and patient counseling must be confirmed with the Bosentan REMS for bosentan to be dispensed to your patient.

- This form may be completed online at **www.BosentanREMSProgram.com**, by calling the Contact Center at 1-866-359-2612 or by faxing at 1-800-730-8231.
- Your patient will not receive a call from the Bosentan REMS during a given month if completion of tests and counseling for that month have been confirmed.
- If this form is not submitted, your patient will receive a call from the Bosentan REMS each month during treatment to confirm completion of required tests and counseling on the risks associated with treatment with bosentan.

Use this form to:

1. Report that a patient has been counseled on the risk of hepatotoxicity.
2. Report pretreatment and monthly liver test completion for a patient in the Bosentan REMS.
3. Report that a female of reproductive potential (as defined in the ***Prescriber Guide***) has been counseled on the risk of embryo-fetal toxicity, as appropriate for the reproductive potential status as defined in the ***Prescriber Guide***.
4. Report pretreatment and monthly pregnancy test completion (including the final test one month following bosentan discontinuation) for a female of reproductive potential in the Bosentan REMS.

If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit **www.BosentanREMSProgram.com**, or call the Bosentan REMS at 1-866-359-2612.

Prescriber Information (All fields required)

First Name:	Last Name:	NPI#:
Phone:	Fax:	Email:

Patient Information (All fields required)

First Name:	Last Name:	
Date of Birth (MM/DD/YYYY):	Zip Code:	Gender: ❒ Male ❒ Female

Is this patient a Female of Reproductive Potential?
(as defined in the ***Prescriber Guide***) ❒ Yes ❒ No

Confirm Liver Test Completed

For all patients: Complete this section to confirm the completion of a liver test

❒ **Monthly liver test has been completed**

By checking the above box, you attest that a liver test has been completed for the patient indicated on this form.

Confirm Pregnancy Test Completed

For females of reproductive potential: Complete this section to confirm the completion of a pregnancy test

❒ **Monthly pregnancy test has been completed**

By checking the above box, you attest that a pregnancy test has been completed for the patient indicated on this form.

Acknowledgement of Patient Counseling

❒ **Patient has been counseled this month on the risks associated with bosentan treatment and the Bosentan REMS requirements**

By checking the above box, you attest that this patient has been counseled this month on the risks of hepatotoxicity and embryo-fetal toxicity, as appropriate for the reproductive potential status as defined in the ***Prescriber Guide***.

Signature

By signing below, you signify that the appropriate test(s) and/or counseling indicated above have been completed for this patient.

Signature:	**Date:**
Print Name:	

Submitted by: ❒Prescriber Designee ❒Prescriber

Please Note: A certified prescriber or prescriber designee may complete and submit this form on behalf of the certified prescriber of record. The certified prescriber of record is responsible for monitoring, evaluating, and managing each patient under their care.

Reference ID: 4976585

Bosentan
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Prescribing Information | Medication Guide

Login

Prescribers | Pharmacies | Patients | Pharmacy Locator | FAQs

Important REMS Update

Please click to open the Important REMS Update

Bosentan Risk Evaluation and Mitigation Strategy (REMS)

Bosentan REMS Overview

- A Risk Evaluation and Mitigation Strategy (REMS) is used to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure the benefits of a drug outweigh its risks
- The Bosentan REMS is a program for brand and generic approved bosentan medications for the treatment of pulmonary arterial hypertension (PAH). Due to the risks of hepatotoxicity and embryo-fetal toxicity, bosentan is only available through the Bosentan REMS
- All healthcare providers must certify in the Bosentan REMS and must comply with the Bosentan REMS requirements in order to prescribe a bosentan product
- All patients must be enrolled in the Bosentan REMS and must comply with the Bosentan REMS requirements in order to receive bosentan:
  - Patients must agree to complete liver tests and pregnancy tests based on the patient's reproductive potential classification prior to receiving bosentan
  - All patients must agree to be counseled on the Bosentan REMS and the risks of treatment with bosentan
  - All patients must agree to be contacted about completing required monthly testing and counseling
- Only inpatient, outpatient, and chain pharmacies certified in the Bosentan REMS can dispense bosentan

Materials for Prescribers

- *Prescriber Enrollment Form*
- *Prescriber Guide*
- *Patient Enrollment Form*
- *Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*
- *Testing and Patient Counseling Reporting Form*
- *Fact Sheet*

Materials for Pharmacies

- *Outpatient Pharmacy Enrollment Form*
- *Chain Pharmacy Headquarters Enrollment Form*
- *Inpatient Pharmacy Enrollment Form*
- *Pharmacy Guide*
- *Fact Sheet*

Materials for Patients

- *Guide for Patients*

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Prescriber Overview

Prescribers must complete the following steps in the Bosentan REMS:

1 READ

- READ the Prescribing Information for bosentan and the ***Prescriber Guide*** to understand the risks of bosentan and to learn about the Bosentan REMS
  - You must understand the risks of bosentan and become familiar with the Bosentan REMS

2 COMPLETE

- COMPLETE a ***Prescriber Enrollment Form***
  - By signing the form, you attest to understanding the risks of bosentan and agree to comply with the requirements of the Bosentan REMS
  - You can complete the ***Prescriber Enrollment Form*** online or download paper copies from the **Bosentan REMS Website** here, and fax the form to the Bosentan REMS at 1-800-730-8231

3 DETERMINE

- DETERMINE the reproductive potential status for female patients
  - You should identify female patients as one of the following categories on the ***Patient Enrollment Form***:
    - **Female of Reproductive Potential**
    - **Female of Non-Reproductive Potential** (choose one of the options below)
      - Pre-pubertal female
      - Post-menopausal female
      - Female with other medical reasons for permanent, irreversible infertility
  - Expanded definitions are provided in the ***Prescriber Guide***

4 EDUCATE & COUNSEL

- EDUCATE & COUNSEL all patients about the risks of bosentan
  - For all patients, you must:
    - Counsel all patients on the risk of hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity and to contact the prescriber if they have any signs or symptoms of liver problems and REMS requirements including the need to complete liver testing and provide the ***Guide for Patients*** to each patient
    - Educate patients about the Bosentan REMS
  - For females of reproductive potential, you must:
    - Counsel patients about the risk of embryo-fetal toxicity, the need to complete monthly pregnancy tests, and the need to use reliable contraception during bosentan treatment, and for one month following treatment discontinuation
    - Counsel the patient to immediately contact the prescriber if the patient misses a menstrual period, suspects that they are pregnant, had unprotected sex, or thinks that their birth control has failed
    - Counsel the patient on the medical options in the event of unprotected sexual intercourse or known or suspected contraception failure
    - Counsel patients who fail to comply with the REMS requirements
  - For pre-pubertal females, you must:
    - Counsel the patient about the risk of embryo-fetal toxicity
    - Counsel the patient to immediately contact the prescriber when the patient begins to menstruate

5 ENROLL

- ENROLL all patients in the Bosentan REMS by completing the ***Patient Enrollment Form*** with the patient
  - Order and review a liver test for all patients, and a pregnancy test for females of reproductive potential
  - Confirm the patient has agreed to comply with the REMS requirements and has signed the form where indicated
  - Complete the form on the **Bosentan REMS Website** here, or fax the completed form to the Bosentan REMS at 1-800-730-8231
  - Keep the original form with the patient's records and provide a completed copy of the form to the patient

6 REVIEW

- REVIEW all required test results and monitor patients throughout treatment
  - For all patients:
    - Order and review liver tests each month during treatment with bosentan
    - Confirm, when necessary, the completion of liver tests and counseling each month by one of the following methods:
      - Entering the testing and counseling information on the **Bosentan REMS Website** here
      - Submitting a ***Testing and Patient Counseling Reporting Form*** by fax to the Bosentan REMS at 1-800-730-8231
      - Calling the Bosentan REMS at 1-866-359-2612
    - For changes in aminotransferase levels, adjust the monitoring and treatment with bosentan
    - Discontinue bosentan if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increase in bilirubin ≥2 x ULN
  - For all females of reproductive potential:
    - Order and review pregnancy tests monthly during treatment with bosentan and for for one month following treatment discontinuation
    - Prescribers may confirm the completion of pregnancy tests and counseling each month by one of the following methods:
      - Entering the testing and counseling information on the **Bosentan REMS Website** here
      - Submitting a ***Testing and Patient Counseling Reporting Form*** by fax to the Bosentan REMS at 1-800-730-8231
      - Calling the Bosentan REMS at 1-866-359-2612
    - Monitor patient's reproductive status during treatment with bosentan and report any change or misclassification in reproductive potential status by submitting a ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** to the Bosentan REMS within 10 business days of becoming aware of the change
      - Prescribers can enter the information on the **Bosentan REMS Website** here or fax the completed form to the Bosentan REMS at 1-800-730-8231
  - For females of non-reproductive potential:
    - Monitor patient's reproductive status during treatment with bosentan and report any change or misclassification in reproductive potential status by submitting a ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** to the Bosentan REMS within 10 business days of becoming aware of the change
      - Prescribers can enter the information on the **Bosentan REMS Website** here or fax the completed form to the Bosentan REMS at 1-800-730-8231
    - For each patient who is 8 years of age or older[1], verify at least annually and report the reproductive status by completing and submitting the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form*** to the Bosentan REMS

Prescriber Designees

Certified prescribers can add prescriber designees on the Bosentan REMS Website

The certified prescriber of record is responsible for compliance with the REMS requirements and ensuring the REMS requirements are being followed by the prescriber designee. The certified prescriber of record is responsible for monitoring, evaluating, and managing of each patient under their care.

- The following activities must be performed by the certified prescriber and cannot be delegated:
  - Completing and submitting a ***Prescriber Enrollment Form***
  - Completing and submitting a ***Patient Enrollment Form***
  - Submitting a change in reproductive potential status or verifying pre-pubertal status annually
  - Granting a Refill Dispense Exception
  - Adding other prescriber designees
- A prescriber can delegate the following activities to a prescriber designee:
  - Updating patient information with the Bosentan REMS after the patient has already been enrolled
  - Confirming completion of patient liver testing and, for females of reproductive potential, pregnancy testing
  - Confirming completion of patient counseling

7 NOTIFY

- NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity

8 REPORT

- REPORT pregnancies to the Bosentan REMS

[1]Clinical threshold for evaluating onset of puberty.

Start Prescriber Certification

Materials for Prescribers

- ***Prescriber Enrollment Form***
- ***Prescriber Guide***
- ***Patient Enrollment Form***
- ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***
- ***Testing and Patient Counseling Reporting Form***
- ***Fact Sheet***

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Prescriber Certification

Bosentan REMS Prescriber Enrollment Form

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit www.BosentanREMSProgram.com, or call the Bosentan REMS at 1-866-359-2612.

Required fields are denoted by "*".

Prescriber Identifier

* **Prescriber NPI#**

Continue

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Prescriber Certification

Bosentan REMS Prescriber Enrollment Form

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

If you have questions, require additional information, or need additional copies of Bosentan REMS documents, visit www.BosentanREMSProgram.com, or call the Bosentan REMS at 1-866-359-2612.

Required fields are denoted by "*".

Prescriber Identifier

*Prescriber NPI#

1234567890

Prescriber Responsibilities

By signing this form, I agree to comply with the following Bosentan REMS requirements:

- Reviewing the Prescribing Information and the ***Prescriber Guide***.
- Enrolling in the Bosentan REMS by completing the ***Prescriber Enrollment Form*** and submitting it to the Bosentan REMS.

Before treatment initiation (first dose), I must:

For all patients:

- Provide the patient a copy of the ***Guide for Patients***.
- Enroll the patient by completing and submitting the ***Patient Enrollment Form*** to the Bosentan REMS. Provide a completed copy to the patient.
- Counsel the patient on the risk of hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity, to contact the prescriber if the patient has any signs or symptoms of liver problems, and program requirements including the need to complete liver testing using the ***Guide for Patients***.
- Assess the patient's liver function. Document and submit to the Bosentan REMS using the ***Patient Enrollment Form***.

For all females:

- Assess the patient's reproductive status using the definitions in the ***Prescriber Guide***. Document and submit to the Bosentan REMS using the ***Patient Enrollment Form***.

For pre-pubertal females:

- Counsel the patient about the risk of embryo-fetal toxicity and the need to immediately contact the prescriber when the patient begins to menstruate using the ***Guide for Patients***.

For females of reproductive potential:

- Counsel the patient about the risk of embryo-fetal toxicity, the need to use reliable contraception as defined in the ***Prescriber Guide*** during treatment and for one month following treatment discontinuation, the need to complete pregnancy testing, the need to contact the prescriber if pregnancy is suspected, and emergency contraception using the ***Guide for Patients***.
- Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results. Document and submit to the Bosentan REMS using the ***Patient Enrollment Form***.

During treatment; monthly, I must:

For all patients:

- Assess the patient's liver function and counsel the patient on the risk of hepatotoxicity.

For females of reproductive potential:

- Counsel the patient on the risk of embryo-fetal toxicity.
- Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results.

During treatment; at least annually, I must:

For pre-pubertal females age 8 years or older:

- Document reproductive status and submit to the Bosentan REMS using the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***.

After treatment discontinuation; for one month, I must:

For females of reproductive potential:

- Assess the patient's pregnancy status by ordering a pregnancy test and reviewing the results.

At all times, I must:

- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.

For pre-pubertal females:

- Assess the patient's reproductive status.

At all times, within 10 business days, I must:

- Report a change or misclassification in reproductive status to the Bosentan REMS using the ***Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form***.

Prescriber Information

*First Name: Steve | MI: | *Last Name: Meru

*Email:

*Professional Designation (select one)
○ MD ○ DO ○ PA ○ NP

*Medical Specialty (select one)
○ Cardiology ○ Pulmonology ○ Rheumatology ○ General/Family Practice ○ Other

*Clinic/Practice Name:

*Address: 100 Main Street

*City: Philadelphia | *State: PA | *Zip Code: 99999

*Preferred Method of Contact (select one)
○ Fax ○ Email

*Office Phone: | Ext: | *Fax: | *Mobile:

Prescriber Signature

By signing below, you signify your understanding of the risks of bosentan treatment and your obligations as a bosentan prescriber to educate your patients about the Bosentan REMS, monitor them appropriately, and report adverse events suggestive of hepatotoxicity and pregnancies to the Bosentan REMS.

☐ *Signature

Cancel | Submit

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Bosentan
REMS Program

Prescribing Information | Medication Guide

Login

Prescribers | Pharmacies | Patients | Pharmacy Locator | FAQs

Bosentan REMS Prescriber Enrollment

The Bosentan REMS will notify you of successful certification and when you can prescribe bosentan.

You will receive an email containing a link to login and instructions for creating a password. Please login with the username provided. You will then be prompted to create a password.

You can assign prescriber designees on the **Bosentan REMS Website** to help with select administrative tasks.

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Types and Definitions

All outpatient, chain, and inpatient pharmacies must certify in the Bosentan REMS to purchase and dispense bosentan.

Pharmacy staff must enroll in the Bosentan REMS to obtain a Pre-Dispense Authorization (PDA) or to perform an inpatient REMS requirements verification on the **Bosentan REMS Website**. For more information on the pharmacy staff enrollment process, please go to Pharmacy Staff Enrollment.

Pharmacies participating in the Bosentan REMS must determine their pharmacy type based on the definitions below:

Pharmacy Type (click a pharmacy type to start Pharmacy Certification)	Description
Outpatient Pharmacy	For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.
Chain Pharmacy	For the purposes of this REMS, chain pharmacy are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.
Inpatient Pharmacy	For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

To become certified, pharmacies must designate an authorized representative to complete enrollment. An authorized representative for a pharmacy may be, but is not limited to:

- Pharmacy Manager
- Staff Pharmacist
- Director of Pharmacy Services
- Corporate Executive overseeing Pharmacy Services

In general, an authorized representative for a pharmacy:

- Trains all relevant staff involved in the dispensing of bosentan on the Bosentan REMS.
- Coordinates the activities required for the pharmacy and/or pharmacy staff in the Bosentan REMS.
- Maintains records of training.
- Maintains records that all processes and procedures are in place and are being followed.
- Complies with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

Note: New authorized representatives must certify in the Bosentan REMS if the authorized representative changes. All pharmacies will be contacted to verify the name and contact information of the pharmacy's authorized representative every 2 years.

OUTPATIENT PHARMACY | CHAIN PHARMACY HEADQUARTERS | INPATIENT PHARMACY

Start Pharmacy Certification

Materials for Pharmacies

- *Outpatient Pharmacy Enrollment Form*
- *Chain Pharmacy Headquarters Enrollment Form*
- *Inpatient Pharmacy Enrollment Form*
- *Pharmacy Guide*
- *Fact Sheet*

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Types and Definitions

All outpatient, chain, and inpatient pharmacies must certify in the Bosentan REMS to purchase and dispense bosentan.

Pharmacy staff must enroll in the Bosentan REMS to obtain a Pre-Dispense Authorization (PDA) or to perform an inpatient REMS requirements verification on the **Bosentan REMS Website**. For more information on the pharmacy staff enrollment process, please go to Pharmacy Staff Enrollment.

Pharmacies participating in the Bosentan REMS must determine their pharmacy type based on the definitions below:

Pharmacy Type (click a pharmacy type to start Pharmacy Certification)	Description
Outpatient Pharmacy	For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.
Chain Pharmacy	For the purposes of this REMS, chain pharmacy are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.
Inpatient Pharmacy	For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

To become certified, pharmacies must designate an authorized representative to complete enrollment. An authorized representative for a pharmacy may be, but is not limited to:

- Pharmacy Manager
- Staff Pharmacist
- Director of Pharmacy Services
- Corporate Executive overseeing Pharmacy Services

In general, an authorized representative for a pharmacy:

- Trains all relevant staff involved in the dispensing of bosentan on the Bosentan REMS.
- Coordinates the activities required for the pharmacy and/or pharmacy staff in the Bosentan REMS.
- Maintains records of training.
- Maintains records that all processes and procedures are in place and are being followed.
- Complies with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

Note: New authorized representatives must certify in the Bosentan REMS if the authorized representative changes. All pharmacies will be contacted to verify the name and contact information of the pharmacy's authorized representative every 2 years.

OUTPATIENT PHARMACY | **CHAIN PHARMACY HEADQUARTERS** | **INPATIENT PHARMACY**

Start Pharmacy Certification

The authorized representative for each outpatient pharmacy must complete the following steps in the Bosentan REMS:

1 READ

- READ the ***Pharmacy Guide*** to understand the risks of bosentan and to learn about the Bosentan REMS
  - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS, prior to certifying their pharmacy

2 ENROLL

- ENROLL the pharmacy by completing the ***Outpatient Pharmacy Enrollment Form***
  - By signing the form, the authorized representative attests to understanding the risks of bosentan and agrees to comply with the Bosentan REMS as described on the ***Outpatient Pharmacy Enrollment Form***
  - The authorized representative can complete the enrollment form online or download paper copies here and fax the form to the Bosentan REMS at 1-800-730-8231

3 TRAIN

- TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS requirements
  - Prior to dispensing bosentan, the authorized representative must ensure that all pharmacy staff who participate in dispensing bosentan are educated on the risks associated with bosentan and the requirements of the Bosentan REMS, including obtaining a Pre-Dispense Authorization (PDA) verifying that safe use conditions are met for the patient prior to dispensing Bosentan, as defined on the ***Outpatient Pharmacy Enrollment Form***
  - Any pharmacy employee may assume the role of pharmacy staff by associating with a certified outpatient pharmacy on the **Bosentan REMS Website**

4 DOCUMENT

- DOCUMENT all staff training
  - Certified pharmacies are subject to audit by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed

5 VERIFY SAFE USE CONDITIONS

- VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan
  - Outpatient pharmacies must dispense bosentan to patients only after obtaining a PDA by calling the Contact Center or accessing the **Bosentan REMS Website**
    - If a PDA is not issued, prior to dispensing bosentan, the outpatient pharmacy may perform the corresponding activity to address the reasons that a PDA was not issued:
      - Contact the prescriber or the Bosentan REMS to indicate the prescriber is not certified and must become certified in the Bosentan REMS before bosentan can be dispensed
      - Contact the prescriber or the Bosentan REMS to notify the prescriber that the patient is not enrolled and must be enrolled in the Bosentan REMS before bosentan can be dispensed
      - If a PDA is not issued because required testing is not confirmed, the outpatient pharmacy can confirm with the patient or prescriber that the testing has been completed and enter this confirmation on the **Bosentan REMS Website** or call the Contact Center
      - If counseling is not confirmed in the Bosentan REMS, a PDA will be issued if all other safe use conditions are met. The outpatient pharmacy must complete counseling prior to dispensing bosentan and confirm completion on the **Bosentan REMS Website** or by calling the Contact Center

6 DISPENSE

- DISPENSE up to a 30 days' supply
  - Up to a 90 days' supply may be dispensed with a refill dispense exception authorized by the prescriber for extended travel outside of the United States of more than 30 days

7 DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN

- DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS

8 NOTIFY

- NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity

9 REPORT

- REPORT pregnancies to the Bosentan REMS

10 HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY

- HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY in the Bosentan REMS if the authorized representative changes

Start Pharmacy Certification

Materials for Pharmacies

- *Outpatient Pharmacy Enrollment Form*
- *Chain Pharmacy Headquarters Enrollment Form*
- *Inpatient Pharmacy Enrollment Form*
- *Pharmacy Guide*
- *Fact Sheet*

Pharmacy Types and Definitions

All outpatient, chain, and inpatient pharmacies must certify in the Bosentan REMS to purchase and dispense bosentan.

Pharmacy staff must enroll in the Bosentan REMS to obtain a Pre-Dispense Authorization (PDA) or to perform an inpatient REMS requirements verification on the **Bosentan REMS Website**. For more information on the pharmacy staff enrollment process, please go to Pharmacy Staff Enrollment.

Pharmacies participating in the Bosentan REMS must determine their pharmacy type based on the definitions below:

Pharmacy Type (click a pharmacy type to start Pharmacy Certification)	Description
Outpatient Pharmacy	For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.
Chain Pharmacy	For the purposes of this REMS, chain pharmacy are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.
Inpatient Pharmacy	For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

To become certified, pharmacies must designate an authorized representative to complete enrollment. An authorized representative for a pharmacy may be, but is not limited to:

- Pharmacy Manager
- Staff Pharmacist
- Director of Pharmacy Services
- Corporate Executive overseeing Pharmacy Services

In general, an authorized representative for a pharmacy:

- Trains all relevant staff involved in the dispensing of bosentan on the Bosentan REMS.
- Coordinates the activities required for the pharmacy and/or pharmacy staff in the Bosentan REMS.
- Maintains records of training.
- Maintains records that all processes and procedures are in place and are being followed.
- Complies with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

Note: New authorized representatives must certify in the Bosentan REMS if the authorized representative changes. All pharmacies will be contacted to verify the name and contact information of the pharmacy's authorized representative every 2 years.

OUTPATIENT PHARMACY | **CHAIN PHARMACY HEADQUARTERS** | **INPATIENT PHARMACY**

Start Pharmacy Certification

The authorized representative for the chain pharmacy headquarters must complete the following steps in the Bosentan REMS:

1 READ
- READ the ***Pharmacy Guide*** to understand the risks of bosentan and to learn about the Bosentan REMS
  - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS, prior to certifying their pharmacy

2 ENROLL
- ENROLL the chain pharmacy by completing the ***Chain Pharmacy Headquarters Enrollment Form***
  - By signing the form, the authorized representative attests to understanding the risks of bosentan and agrees to comply with the Bosentan REMS as described in the ***Chain Pharmacy Headquarters Enrollment Form***
  - The authorized representative can complete the enrollment form online or download paper copies of the form here and fax the form to the Bosentan REMS at 1-800-730-8231

3 TRAIN
- TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS requirements
  - Prior to dispensing bosentan, the authorized representative must ensure that all pharmacy staff who participate in dispensing bosentan are educated on the risks associated with bosentan and the requirements of the Bosentan REMS, including obtaining a Pre-Dispense Authorization (PDA) verifying that safe use conditions are met for the patient prior to dispensing bosentan, as defined on the ***Chain Pharmacy Headquarters Enrollment Form***
  - Any pharmacy employee may assume the role of pharmacy staff by associating with a certified chain pharmacy on the **Bosentan REMS Website**

4 DOCUMENT
- DOCUMENT all staff training
  - Once each dispensing location is trained, it is the authorized representative's responsibility to report confirmation of training to the Bosentan REMS online through the **Bosentan REMS Website**, or by calling the Contact Center at 1-866-359-2612 to obtain instructions on providing a list of trained pharmacy locations. Once the Bosentan REMS confirms the required dispensing information, the dispensing location will be authorized to purchase, receive, and dispense bosentan
  - Certified pharmacies are subject to audit by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed

5 VERIFY SAFE USE CONDITIONS
- VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan
  - Chain pharmacies must dispense bosentan to patients only after obtaining a PDA by calling the Contact Center or accessing the **Bosentan REMS Website**
    - If a PDA is not issued, prior to dispensing bosentan, the pharmacy may perform the corresponding activity to address the reasons that a PDA was not issued:
      - Contact the prescriber or the Bosentan REMS to indicate that the prescriber is not certified and must become certified in the Bosentan REMS before bosentan can be dispensed
      - Contact the prescriber or the Bosentan REMS to notify the prescriber that the patient is not enrolled and must be enrolled in the Bosentan REMS before bosentan can be dispensed
      - If a PDA is not issued because required testing is not confirmed, the pharmacy can confirm with the patient or prescriber that the testing has been completed and enter this confirmation on the **Bosentan REMS Website** or call the Contact Center
      - If counseling is not confirmed in the Bosentan REMS, a PDA will be issued if all other safe use conditions are met. The pharmacy must complete counseling prior to dispensing bosentan and can confirm completion on the **Bosentan REMS Website** or by calling the Contact Center

6 DISPENSE
- DISPENSE up to a 30 days' supply
  - Up to a 90 days' supply may be dispensed with a refill dispense exception authorized by the prescriber for extended travel outside of the United States of more than 30 days

7 DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN
- DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS

8 NOTIFY
- NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity

9 REPORT
- REPORT pregnancies to the Bosentan REMS

10 HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY
- HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY in the Bosentan REMS if the authorized representative changes

Start Pharmacy Certification

Materials for Pharmacies

- *Outpatient Pharmacy Enrollment Form*
- *Chain Pharmacy Headquarters Enrollment Form*
- *Inpatient Pharmacy Enrollment Form*
- *Pharmacy Guide*
- *Fact Sheet*

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Types and Definitions

All outpatient, chain, and inpatient pharmacies must certify in the Bosentan REMS to purchase and dispense bosentan.

Pharmacy staff must enroll in the Bosentan REMS to obtain a Pre-Dispense Authorization (PDA) or to perform an inpatient REMS requirements verification on the **Bosentan REMS Website**. For more information on the pharmacy staff enrollment process, please go to Pharmacy Staff Enrollment.

Pharmacies participating in the Bosentan REMS must determine their pharmacy type based on the definitions below:

Pharmacy Type (click a pharmacy type to start Pharmacy Certification)	Description
Outpatient Pharmacy	For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.
Chain Pharmacy	For the purposes of this REMS, chain pharmacy are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.
Inpatient Pharmacy	For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

To become certified, pharmacies must designate an authorized representative to complete enrollment. An authorized representative for a pharmacy may be, but is not limited to:

- Pharmacy Manager
- Staff Pharmacist
- Director of Pharmacy Services
- Corporate Executive overseeing Pharmacy Services

In general, an authorized representative for a pharmacy:

- Trains all relevant staff involved in the dispensing of bosentan on the Bosentan REMS.
- Coordinates the activities required for the pharmacy and/or pharmacy staff in the Bosentan REMS.
- Maintains records of training.
- Maintains records that all processes and procedures are in place and are being followed.
- Complies with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

Note: New authorized representatives must certify in the Bosentan REMS if the authorized representative changes. All pharmacies will be contacted to verify the name and contact information of the pharmacy's authorized representative every 2 years.

OUTPATIENT PHARMACY | **CHAIN PHARMACY HEADQUARTERS** | **INPATIENT PHARMACY**

Start Pharmacy Certification

The authorized representative for each inpatient pharmacy must complete the following steps in the Bosentan REMS:

1 READ

- READ the ***Pharmacy Guide*** to understand the risks of bosentan and to learn about the Bosentan REMS
  - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS, prior to certifying their pharmacy

2 ENROLL

- ENROLL the pharmacy by completing the ***Inpatient Pharmacy Enrollment Form***
  - By signing the form, the authorized representative attests to understanding the risks of bosentan and agrees to comply with the Bosentan REMS as described on the ***Inpatient Pharmacy Enrollment Form***
  - The authorized representative can complete the enrollment form online or download paper copies of the form here and fax the form to the Bosentan REMS at 1-800-730-8231

3 TRAIN

- TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS requirements
  - Prior to dispensing bosentan, the authorized representative must ensure that all staff are appropriately trained on the Bosentan REMS procedures and materials as defined on the ***Inpatient Pharmacy Enrollment Form***
  - Any pharmacy employee may assume the role of pharmacy staff by associating with a certified inpatient pharmacy on the **Bosentan REMS Website** to verify safe use conditions for each patient prior to dispensing bosentan

4 DOCUMENT

- DOCUMENT all staff training
  - Certified pharmacies are subject to audit by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed

5 VERIFY SAFE USE CONDITIONS

- VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan
  - Dispense bosentan to patients only after calling the Contact Center, accessing the **Bosentan REMS Website**, or accessing the patient's medical record to:
    - Verify the patient is under the supervision of a prescriber who is certified
    - Verify the patient is enrolled or will be enrolled prior to discharge
    - Verify counseling is complete
    - Verify liver testing and pregnancy testing (for females of reproductive potential) is complete

6 DISPENSE

- DISPENSE no more than a 15-days' supply of bosentan at discharge

7 DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN

- DO NOT DISTRIBUTE, TRANSFER, LOAN, OR SELL BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS

8 NOTIFY

- NOTIFY the Bosentan REMS of adverse events suggestive of hepatotoxicity

9 REPORT

- REPORT pregnancies to the Bosentan REMS

10 HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY

- HAVE ANY NEW AUTHORIZED REPRESENTATIVE CERTIFY in the Bosentan REMS if the authorized representative changes

Start Pharmacy Certification

Materials for Pharmacies

- *Outpatient Pharmacy Enrollment Form*
- *Chain Pharmacy Headquarters Enrollment Form*
- *Inpatient Pharmacy Enrollment Form*
- *Pharmacy Guide*
- *Fact Sheet*

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Certification

Bosentan REMS Pharmacy Enrollment Form

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

Required fields are denoted by "*".

Pharmacy Type

*I am an

- ◯ Authorized Representative for an Outpatient Pharmacy
- ◯ Authorized Representative for a Chain Pharmacy Headquarters
- ◯ Authorized Representative for an Inpatient Pharmacy

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Certification

Bosentan REMS Pharmacy Enrollment Form - Outpatient Pharmacy

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

Required fields are denoted by "*".

Pharmacy Type

*I am an

- (●) Authorized Representative for an Outpatient Pharmacy
- ( ) Authorized Representative for a Chain Pharmacy Headquarters
- ( ) Authorized Representative for an Inpatient Pharmacy

For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies. An authorized representative of an outpatient pharmacy is responsible for ensuring certification of the pharmacy in the Bosentan REMS.

The authorized representative is also responsible for coordinating the activities required for the pharmacy and pharmacy staff in the Bosentan REMS.

Pharmacy Identifiers

*NPI Number

*DEA Number

*NCPDP Number

Cancel | Continue

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Certification

Bosentan REMS Pharmacy Enrollment Form - Outpatient Pharmacy

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

Required fields are denoted by "*".

Pharmacy Type

*I am an
- (•) Authorized Representative for an Outpatient Pharmacy
- ( ) Authorized Representative for a Chain Pharmacy Headquarters
- ( ) Authorized Representative for an Inpatient Pharmacy

For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies. An authorized representative of an outpatient pharmacy is responsible for ensuring certification of the pharmacy in the Bosentan REMS.

The authorized representative is also responsible for coordinating the activities required for the pharmacy and pharmacy staff in the Bosentan REMS.

Pharmacy Identifiers

*NPI Number	*DEA Number	*NCPDP Number
123456789	99999	987654

Authorized Representative Responsibilities.

I am the authorized representative designated by my pharmacy to oversee implementation of and compliance with the Bosentan REMS. I attest to understanding the Bosentan REMS requirements, and accept responsibility to:

As the Authorized Pharmacy Representative, I must:

- Review the ***Pharmacy Guide***.
- Enroll in the Bosentan REMS by completing the ***Outpatient Pharmacy Enrollment Form*** and submitting it to the Bosentan REMS.
- Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the ***Pharmacy Guide***.

Before dispensing, my pharmacy must:

For all patients:

- Obtain authorization to dispense each prescription by contacting the Bosentan REMS to verify:
  - the patient is enrolled,
  - the prescriber is certified,
  - the pharmacy is certified,
  - if counseling is complete,
  - liver testing is complete,
  - the reproductive status has not changed for female patients, and
  - the pregnancy test is completed for females of reproductive potential or the prescriber authorizes the refill.
- Dispense no more than a 30 days' supply.

For patients without documented testing:

- Communicate with the patient or prescriber to confirm testing.
- Document and submit the confirmation of testing using the Bosentan REMS Website or by calling the Contact Center.

For all patients without documented counseling on hepatotoxicity:

- Counsel the patient on the risk of hepatotoxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

For females of reproductive potential and pre-pubertal females without documented counseling on embryo-fetal toxicity:

- Counsel the patient on the risk of embryo-fetal toxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

At all times my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.
- Not distribute, transfer, loan, or sell bosentan, except to certified dispensers.
- Maintain records of
  - dispensing,
  - training, and
  - that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.
- Have the new authorized representative certify in the Bosentan REMS by completing the ***Outpatient Pharmacy Enrollment Form*** if the authorized representative changes.

Pharmacy Information

*Pharmacy Name
ABC Pharmacy

*Address
100 Main Street

*City	*State	*Zip Code
Philadelphia	PA	

*Phone	*Fax

Authorized Representative Information

*First Name	*Last Name

*Credentials (select one)
( ) RPh ( ) PharmD ( ) BCPS ( ) Other

*Office Phone	*Fax	*Email

*Preferred Method of Contact (select one)
( ) Fax ( ) Email

Authorized Representative Signature

By signing below, you signify your understanding of the risks of bosentan treatment, your obligations as a pharmacy certified in the Bosentan REMS as outlined above, and you agree to oversee the implementation of and compliance with the Bosentan REMS requirements for this pharmacy.

[ ] *Signature

Cancel Submit

Pharmacy Certification

Bosentan REMS Pharmacy Enrollment Form - Chain Pharmacy Headquarters

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

Required fields are denoted by "*".

Pharmacy Type

*I am an

- ○ Authorized Representative for an Outpatient Pharmacy
- ◉ Authorized Representative for a Chain Pharmacy Headquarters
- ○ Authorized Representative for an Inpatient Pharmacy

For the purposes of this REMS, chain pharmacies are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.

The authorized representative is also responsible for reporting confirmation of pharmacy dispensing location training to the Bosentan REMS.

Cancel Continue

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Certification

Bosentan REMS Pharmacy Enrollment Form - Chain Pharmacy Headquarters

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

Required fields are denoted by ***.

Pharmacy Type

***I am an**

- ○ Authorized Representative for an Outpatient Pharmacy
- ◉ Authorized Representative for a Chain Pharmacy Headquarters
- ○ Authorized Representative for an Inpatient Pharmacy

For the purposes of this REMS, chain pharmacies are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.

The authorized representative is also responsible for reporting confirmation of pharmacy dispensing location training to the Bosentan REMS.

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to oversee implementation of and compliance with the Bosentan REMS. I attest to understanding the Bosentan REMS requirements, and accept responsibility to:

As the Authorized Pharmacy Representative, I must:

- Review the ***Pharmacy Guide***
- Enroll in the Bosentan REMS by completing the ***Chain Pharmacy Headquarters Enrollment Form*** and submitting it to the Bosentan REMS.
- Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the ***Pharmacy Guide*** and report confirmation of training for each dispensing location to the Bosentan REMS.

Before dispensing, my pharmacy must:

For all patients:

- Obtain authorization to dispense each prescription by contacting the Bosentan REMS to verify:
  - the patient is enrolled,
  - the prescriber is certified,
  - the pharmacy is certified,
  - if counseling is complete,
  - liver testing is complete,
  - the reproductive status has not changed for female patients, and
  - the pregnancy test is completed for females of reproductive potential or the prescriber authorizes the refill.
- Dispense no more than a 30 days' supply.

For patients without documented testing:

- Communicate with the patient or prescriber to confirm testing.
- Document and submit the confirmation of testing using the Bosentan REMS Website or by calling the Contact Center.

For all patients without documented counseling on hepatotoxicity:

- Counsel the patient on the risk of hepatotoxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

For females of reproductive potential and pre-pubertal females without documented counseling on embryo-fetal toxicity:

- Counsel the patient on the risk of embryo-fetal toxicity.
- Document and submit the confirmation of counseling using the Bosentan REMS Website or by calling the Contact Center.

At all times my pharmacy must:

- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.
- Not distribute, transfer, loan, or sell bosentan, except to certified dispensers.
- Maintain records of
  - dispensing,
  - training, and
  - that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.
- Have the new authorized representative certify in the Bosentan REMS by completing the ***Chain Pharmacy Headquarters Enrollment Form*** if the authorized representative changes.

Chain Pharmacy Headquarters Information

***Pharmacy Name**

***Address**

***City** | ***State** (-- Please Select --) | ***Zip Code** (99999)

***Phone** | ***Fax**

Authorized Representative Information

***First Name** | ***Last Name**

***Credentials (select one)**

○ RPh ○ PharmD ○ BCPS ○ Other

***Office Phone** | ***Fax** | ***Email**

***Preferred Method of Contact (select one)**

○ Fax ○ Email

Authorized Representative Signature

By signing below, you signify your understanding of the risks of bosentan treatment, your obligations as a pharmacy certified in the Bosentan REMS as outlined above, and you agree to oversee the implementation of and compliance with the Bosentan REMS requirements for this pharmacy.

☐ *Signature

Cancel | Submit

Next Steps

1. Once this form is processed, you will receive a pharmacy certification confirmation. Upon receipt, your chain pharmacy headquarters is certified and your dispensing locations are now eligible to complete their training.
2. Once each dispensing location is trained, it is your responsibility to report confirmation of training to the Bosentan REMS online through **www.BosentanREMSProgram.com**, or by calling the Contact Center at 1-866-359-2612 to obtain instructions on providing a list of trained pharmacy locations. Once the Bosentan REMS confirms the required dispensing information, the dispensing location will be authorized to purchase, receive, and dispense bosentan.

For additional information about the Bosentan REMS, please call 1-866-359-2612.

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Bosentan REMS Pharmacy Enrollment

Pharmacy enrollment submitted successfully.

Once this form is processed, you will receive a pharmacy certification confirmation. Upon receipt, your chain pharmacy headquarters is certified and your dispensing locations are now eligible to complete their training.

Once each dispensing location is trained, it is your responsibility to report confirmation of training to the Bosentan REMS online through **www.BosentanREMSProgram.com**, or by calling the Contact Center at 1-866-359-2612 to obtain instructions on providing a list of trained pharmacy locations. Once the Bosentan REMS confirms the required dispensing information, the dispensing location will be authorized to purchase, receive, and dispense bosentan.

Continue

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Certification

Bosentan REMS Pharmacy Enrollment Form - Inpatient Pharmacy

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

Required fields are denoted by "*".

Pharmacy Type

*I am an

- ○ Authorized Representative for an Outpatient Pharmacy
- ○ Authorized Representative for a Chain Pharmacy Headquarters
- ◉ Authorized Representative for an Inpatient Pharmacy

For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

An authorized representative of an inpatient pharmacy is responsible for ensuring certification and training of the pharmacy location, training of the pharmacy staff, and audit readiness.

Pharmacy Identifiers

Please enter NPI Number, DEA Number or NCPDP Number (at least one is required)

*NPI Number

*DEA Number

*NCPDP Number

Cancel Continue

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Certification

Bosentan REMS Pharmacy Enrollment Form - Inpatient Pharmacy

Instructions

Upon completion of these steps, the Bosentan REMS will notify you of successful certification.

Required fields are denoted by "*".

Pharmacy Type

*I am an

- ○ Authorized Representative for an Outpatient Pharmacy
- ○ Authorized Representative for a Chain Pharmacy Headquarters
- ◉ Authorized Representative for an Inpatient Pharmacy

For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

An authorized representative of an inpatient pharmacy is responsible for ensuring certification and training of the pharmacy location, training of the pharmacy staff, and audit readiness.

Pharmacy Identifiers

Please enter NPI Number, DEA Number or NCPDP Number (at least one is required)

*NPI Number	DEA Number	NCPDP Number
1234567890		

Authorized Representative Responsibilities

I am the authorized representative designated by my pharmacy to oversee implementation of and compliance with the Bosentan REMS. I attest to understanding the Bosentan REMS requirements, and accept responsibility to:

As the Authorized Pharmacy Representative, I must:

- Review the ***Pharmacy Guide***.
- Enroll in the Bosentan REMS by completing the ***Inpatient Pharmacy Enrollment Form*** and submitting it to the Bosentan REMS.
- Train all relevant staff involved in dispensing bosentan on the Bosentan REMS requirements using the ***Pharmacy Guide***.
- Establish processes and procedures to verify:
  - the patient is enrolled or will be enrolled prior to discharge,
  - the patient is under the care of a certified prescriber,
  - counseling is complete,
  - liver testing is complete, and
  - pregnancy testing is complete (for females of reproductive potential).

Before dispensing, my pharmacy must:

- Verify the patient:
  - is enrolled or will be prior to discharge,
  - is under the care of a certified prescriber,
  - counseling is complete,
  - completed liver testing, and
  - completed pregnancy testing (for females of reproductive potential).

At all times, my pharmacy must:

- Have the new authorized representative certify in the Bosentan REMS by completing the ***Inpatient Pharmacy Enrollment Form*** if the authorized representative changes.
- Report adverse events suggestive of hepatotoxicity to the Bosentan REMS.
- Report pregnancies to the Bosentan REMS.
- Not distribute, transfer, loan, or sell bosentan, except to certified dispensers.
- Maintain records of training.
- Maintain records that all processes and procedures are in place and are being followed.
- Comply with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed.

At discharge, my pharmacy must:

- Dispense no more than a 15 days' supply.

Pharmacy Information

*Institution or Healthcare Setting Name

*Address
100 Main Street

*City	*State	*Zip Code
Philadelphia	PA	99999

*Phone	*Fax

Authorized Representative Information

*First Name	*Last Name

*Credentials (select one)
○ RPh ○ PharmD ○ BCPS ○ Other

*Office Phone	*Fax	*Email

*Preferred Method of Contact (select one)
○ Fax ○ Email

Authorized Representative Signature

By signing below, you signify your understanding of the risks of bosentan treatment, your obligations as a pharmacy certified in the Bosentan REMS as outlined above, and you agree to oversee the implementation of and compliance with the Bosentan REMS requirements for this pharmacy.

☐ *Signature

Cancel Submit

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Bosentan REMS Pharmacy Enrollment

The Bosentan REMS will notify you of successful certification and when you can prescribe bosentan.

You will receive an email containing a link to login and instructions for creating a password. Please login with the username provided. You will then be prompted to create a password.

You will need to share the Pharmacy ID provided to you for your pharmacy staff to complete their enrollment and associate to your pharmacy.

Continue

For additional information about the Bosentan REMS, please call 1-866-359-2612.

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Pharmacy Staff

Pharmacy Staff may include pharmacists or other individuals who assist in dispensing medication in a pharmacy. If your pharmacy is certified to dispense bosentan, pharmacy staff can enroll in the Bosentan REMS to have access to the **Bosentan REMS Website**. Pharmacy Staff can associate to one or more certified pharmacy locations in the Bosentan REMS through the **Bosentan REMS Website**. Pharmacy Staff enroll by creating an online account.

For Outpatient and Chain Pharmacies:

Once a pharmacy staff member enrolls by creating an online account they can request a Pre-Dispense Authorization (PDA) and reverse a PDA through the **Bosentan REMS Website**. Pharmacy staff members can also enter confirmation of liver tests, pregnancy tests (if applicable) and counseling.

For Inpatient Pharmacies:

Once a pharmacy staff member enrolls by creating an online account they can check inpatient REMS requirements through the **Bosentan REMS Website**.

Start Pharmacy Staff Enrollment

For additional information about the Bosentan REMS, please call 1-866-359-2612.

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Pharmacy Staff Enrollment

Upon completion of these steps, the Bosentan REMS will notify you of your enrollment.

Required fields are denoted by "*".

Pharmacy Identifier

Please contact the Authorized Representative for your pharmacy if you do not know your Pharmacy Identifier.

***Pharmacy ID**

Cancel | Continue

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Pharmacy Staff Enrollment

Upon completion of these steps, the Bosentan REMS will notify you of your enrollment.

Required fields are denoted by "*".

Pharmacy Identifier

Please contact the Authorized Representative for your pharmacy if you do not know your Pharmacy Identifier.

***Pharmacy ID**

1111

Pharmacy Staff Responsibilities

1. I attest that I have been trained and will follow the requirements of the Bosentan REMS as outlined in the ***Pharmacy Guide***
2. I understand I can access the **Bosentan REMS Website** to:
   a. Check inpatient REMS requirements for a patient to receive bosentan (only applies to inpatient pharmacies)
   b. Obtain a Pre-Dispense Authorization (only applies to outpatient pharmacies)
   c. Reverse a Pre-Dispense Authorization (only applies to outpatient pharmacies)
   d. Edit your profile information
   e. Associate your profile to one or more pharmacies
   f. Disassociate your profile from a pharmacy
3. I agree not to share my login credentials for the **Bosentan REMS Website** or allow others to sign into the website using my credentials

As part of your enrollment, you must select the certified pharmacy location(s) where you fill and/or dispense bosentan. It is your responsibility to update this information as necessary.

Pharmacy Staff Information

You are enrolling for the below pharmacy. If this pharmacy is incorrect, please check the Pharmacy ID and if in error, click "Cancel".

11111 - ABC Pharmacy

123 Main Street
Philadelphia, PA 99999

*First Name	*Last Name	*Email

*Phone	Ext	*Fax

***Preferred Method of Contact**

◯ Email ◯ Fax

Cancel Submit

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Patients

What is the Bosentan REMS (Risk Evaluation and Mitigation Strategy)?

The Bosentan REMS tells patients and healthcare providers about **the risks of liver damage and serious birth defects** when taking bosentan. This REMS is required by the Food and Drug Administration (FDA). All patients must enroll in the Bosentan REMS to receive bosentan.

How do I enroll in the Bosentan REMS?

You must complete the following steps to enroll in the Bosentan REMS:

1 READ

READ the ***Guide for Patients*** and the Medication Guide which may come with your prescription

2 ASK

ASK your healthcare provider any questions you have about taking bosentan and the Bosentan REMS

3 UNDERSTAND

MAKE SURE YOU UNDERSTAND

- The benefits and risks of bosentan
- How to enroll and take part in the Bosentan REMS

4 COMPLETE AND SIGN

COMPLETE AND SIGN the ***Patient Enrollment Form*** with your prescriber. Your prescriber will fill out most of the enrollment form for you. You must read and agree to the requirements, then sign to show you understand and will follow the rules of the REMS. Your prescriber will then send the form to the Bosentan REMS. A parent/legal guardian may sign the form for you.

Materials for Patients

Guide for Patients

For additional information about the Bosentan REMS, please call 1-866-359-2612.

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Certified Pharmacy Locator

* **Please select a certified pharmacy type**

○ Inpatient Pharmacy ○ Chain Pharmacy ○ Outpatient Pharmacy

For additional information about the Bosentan REMS Program, please call 1-866-359-2612.

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Certified Pharmacy Locator

*Please select a certified pharmacy type

(•) Inpatient Pharmacy ( ) Chain Pharmacy ( ) Outpatient Pharmacy

Please enter a street address, city, state, or zip code you would like to search for.

*Find a Certified Pharmacy Near:

*Search Radius:

Within 25 miles

Search

For additional information about the Bosentan REMS, please call 1-866-359-2612.

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Certified Pharmacy Locator Results

*Please select a certified pharmacy type

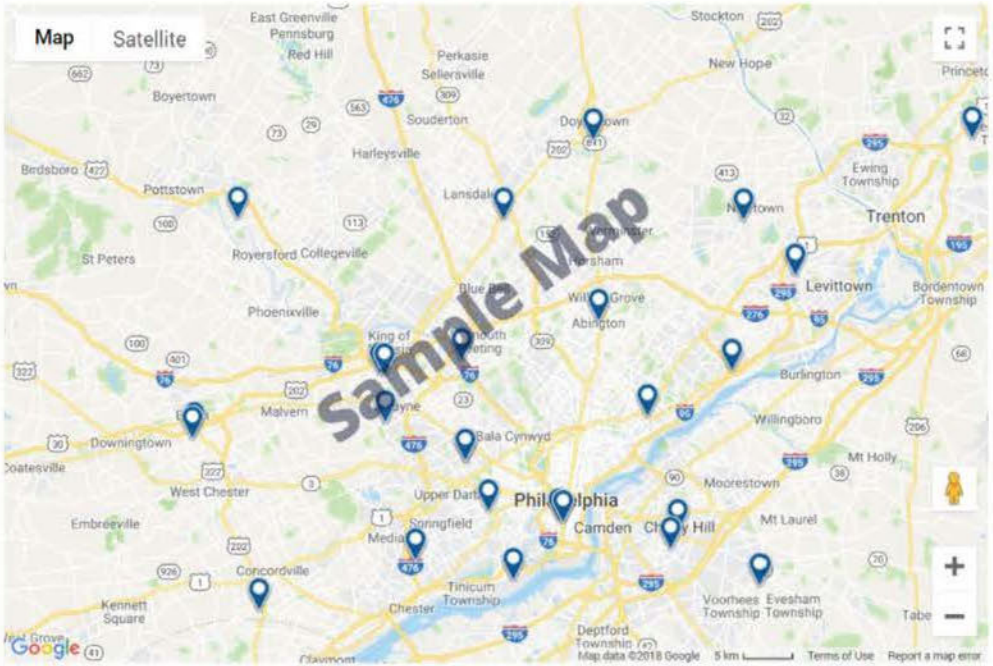
(●) Inpatient Pharmacy ( ) Chain Pharmacy ( ) Outpatient Pharmacy

Please enter a street address, city, state, or zip code you would like to search for.

*Find a Certified Pharmacy Near: 12345

*Search Radius: Within 25 miles

Search



INPATIENT PHARMACY NAME 75.1 miles Directions
100 Main St
Blue Bell, PA 19422
555 555-1212

INPATIENT PHARMACY NAME 75.6 miles Directions
100 Main St
Blue Bell, PA 19422
555 555-1212

INPATIENT PHARMACY NAME 75.6 miles Directions
100 Main St
Blue Bell, PA 19422
555 555-1212

INPATIENT PHARMACY NAME 75.6 miles Directions
100 Main St
Blue Bell, PA 19422
555 555-1212

INPATIENT PHARMACY NAME 76.2 miles Directions
100 Main St
Blue Bell, PA 19422

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Reference ID: 4976585

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Certified Pharmacy Locator

*Please select a certified pharmacy type

○ Inpatient Pharmacy ○ Chain Pharmacy ◉ Outpatient Pharmacy

Certified Outpatient Pharmacies

Pharmacy Name	Phone Number
ABC Pharmacy	555 555-1212

For additional information about the Bosentan REMS, please call 1-866-359-2612.

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Frequently Asked Questions (FAQs)

General | Prescriber | Pharmacy | Patient Management

What is a REMS?

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) to ensure the benefits of a drug outweigh its risks. The Bosentan Applicants have worked with the FDA to develop the Bosentan REMS to mitigate the risks of hepatotoxicity and embryo-fetal toxicity.

What is the Bosentan REMS?

The Bosentan REMS is a program for brand and generic bosentan medication for the treatment of pulmonary arterial hypertension (PAH). Due to the risks of hepatotoxicity and embryo-fetal toxicity, bosentan is only available through the Bosentan REMS.

What is the goal of the Bosentan REMS?

The goal of the Bosentan REMS is to mitigate the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan by:

- Ensuring **prescribers** are educated on the following:
  - the risks of hepatotoxicity and embryo-fetal toxicity
- Ensuring **prescribers** are educated on and adhere to the following:
  - counseling patients about these risks and the need for monthly monitoring
  - enrolling patients in the Bosentan REMS
  - monitoring patients at baseline and monthly
- Ensuring that **pharmacies** are educated on the following:
  - the risks of hepatotoxicity and embryo-fetal toxicity
- Ensuring that **pharmacies** are educated on and adhere to the following:
  - confirming that the appropriate patient monitoring and counseling has occurred before dispensing bosentan
- Ensuring that **patients** are informed about:
  - the risks of hepatotoxicity and embryo-fetal toxicity
  - appropriate baseline and monthly patient monitoring
  - appropriate contraception

What are the different roles of healthcare staff in the Bosentan REMS?

There are four different roles in the Bosentan REMS:

- Prescriber
- Prescriber Designee
- Pharmacy Authorized Representative
- Pharmacy Staff

The high-level certification requirements for each role are presented in the table below.

Role	Description
Prescriber	Prescriber Certification Process • Review the Prescribing Information for bosentan. • Review the ***Prescriber Guide***. • Enroll in the Bosentan REMS by completing the ***Prescriber Enrollment Form*** online here, by submitting via fax to 1-800-730-8231, or mail to the Bosentan REMS at 200 Pinecrest Plaza Morgantown, WV 26505.
Prescriber Designee	Addition of a Prescriber Designee(s) • Be educated on the REMS requirements by the prescriber. • Certified prescribers can add prescriber designee(s) on the **Bosentan REMS Website**.
Authorized Representative (Outpatient Pharmacy)	Authorized Representative Certification Process • Review the ***Pharmacy Guide***. • Authorized representatives for individual pharmacy locations that dispense bosentan for outpatient use, such as retail, specialty, and mail order, must complete and submit the ***Outpatient Pharmacy Enrollment Form*** online here, by submitting via fax to 1-800-730-8231, or mailing to the Bosentan REMS at 200 Pinecrest Plaza Morgantown, WV 26505.
Authorized Representative (Chain Pharmacy)	Chain Pharmacy Authorized Representative Certification Process • Review the ***Pharmacy Guide***. • Authorized representatives for multiple location retail pharmacies that dispense bosentan for outpatient use, and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS, must complete and submit the ***Chain Pharmacy Headquarters Enrollment Form*** online here, by submitting via fax to 1-800-730-8231, or by mailing to the Bosentan REMS at 200 Pinecrest Plaza Morgantown, WV 26505.
Authorized Representative (Inpatient Pharmacy)	Authorized Representative Certification Process • Review the ***Pharmacy Guide***. • Authorized representatives for pharmacy locations that dispense bosentan for inpatient use, such as pharmacies in hospitals, hospices, long-term care facilities, and prisons, must complete and submit the ***Inpatient Pharmacy Enrollment Form*** online here, by submitting via fax to 1-800-730-8231, or by mailing to the Bosentan REMS at 200 Pinecrest Plaza Morgantown, WV 26505.
Pharmacy Staff	Pharmacy Staff Enrollment Process • Be trained on the Bosentan REMS by your pharmacy's authorized representative. • Enroll as pharmacy staff on the **Bosentan REMS Website** here.

What are the hours of the Contact Center?

The Contact Center (1-866-359-2612) hours of operation are Monday through Friday, 8 AM to 8 PM Eastern Time.

Stakeholders can access the **Bosentan REMS Website** at www.BosentanREMSProgram.com 24 hours a day, 7 days a week.

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Frequently Asked Questions (FAQs)

General | Prescriber | Pharmacy | Patient Management

How can a prescriber become certified in the Bosentan REMS?

Prescribers can certify in the Bosentan REMS by completing the ***Prescriber Enrollment Form*** online here, by submitting it to the Bosentan REMS by fax at 1-800-730-8231 or by mailing it to the Bosentan REMS at 200 Pinecrest Plaza Morgantown, WV 26505.

Who can certify as a prescriber in the Bosentan REMS?

Any medical professional prescribing bosentan must become certified in the Bosentan REMS prior to prescribing bosentan.

Can a prescriber delegate REMS responsibilities to another member of their staff?

A prescriber can designate specific office staff members to assist them in the following activities:

- Updating patient information with the Bosentan REMS after the patient has already been enrolled
- Confirming completion of liver tests and/or pregnancy tests and patient counseling

The following activities must be performed by the certified prescriber and cannot be delegated:

- Completing and submitting a ***Prescriber Enrollment Form***
- Completing and submitting a ***Patient Enrollment Form***
- Submitting a change in reproductive potential status or verifying pre-pubertal status annually
- Granting a Refill Dispense Exception
- Adding other prescriber designees

Certified prescribers can add prescriber designees on the **Bosentan REMS Website**. These designees may complete the above referenced activities, but the certified prescriber of record is responsible for compliance with the REMS requirements, including monitoring, evaluating, and managing each patient under their care.

How can a prescriber find pharmacies that are certified in the Bosentan REMS?

A prescriber can find certified pharmacies by calling the Contact Center at 1-866-359-2612 or by utilizing the "Pharmacy Locator" feature on the **Bosentan REMS Website** here.

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Frequently Asked Questions (FAQs)

General | Prescriber | Pharmacy | Patient Management

What are the different pharmacy certification types in the Bosentan REMS?

All inpatient, outpatient, and chain pharmacies must certify in the Bosentan REMS to purchase and dispense bosentan.

Pharmacies participating in the Bosentan REMS must determine the company's pharmacy type based on the definitions below:

Pharmacy Type	Description
Outpatient Pharmacy	For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.
Chain Pharmacy	For the purposes of this REMS, chain pharmacies are retail pharmacies with multiple locations that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS.
Inpatient Pharmacy	For the purposes of this REMS, inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

How does a pharmacy certify in the Bosentan REMS?

Outpatient Pharmacy

Authorized Representative Certification Process

- Review the ***Pharmacy Guide***
- Authorized representatives for individual pharmacy locations that dispense bosentan for outpatient use, such as retail, specialty, and mail order, must complete and submit the ***Outpatient Pharmacy Headquarters Enrollment Form*** online here, by submitting via fax to 1-800-730-8231, or by mailing it to the Bosentan REMS at 200 Pinecrest Plaza Morgantown, WV 26505.

Chain Pharmacy

Chain Pharmacy Authorized Representative Certification Process

- Review the ***Pharmacy Guide***
- Authorized representatives for multiple location retail pharmacies that dispense bosentan for outpatient use and have a pharmacy headquarters that coordinates pharmacy enrollment in the Bosentan REMS, must complete and submit the ***Chain Pharmacy Headquarters Enrollment Form*** online here, by submitting via fax to 1-800-730-8231, or by mailing it to the Bosentan REMS 200 Pinecrest Plaza Morgantown, WV 26505.

Inpatient Pharmacy

Authorized Representative Certification Process

- Review the ***Pharmacy Guide***
- Authorized representatives for pharmacy locations that include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons, must complete and submit the ***Inpatient Pharmacy Enrollment Form*** online here, by submitting via fax to 1-800-730-8231, or by mailing it to the Bosentan REMS 200 Pinecrest Plaza Morgantown, WV 26505.

What is an authorized representative?

In general, an authorized representative for a pharmacy:

- Trains all relevant staff involved in the dispensing of bosentan on the Bosentan REMS requirements as described in the **Pharmacy Guide** and maintains a record of the training
- Coordinates the activities required for the pharmacy and/or pharmacy staff in the Bosentan REMS
- Maintains records of training
- Maintains documentation that all processes and procedures are in place and are being followed
- Complies with audits carried out by the manufacturers or a third party acting on behalf of the manufacturers to ensure that all processes and procedures are in place and are being followed

How do closed healthcare system pharmacies, such as the Veterans Administration (VA), certify in the Bosentan REMS?

Closed healthcare system pharmacies certify in the Bosentan REMS, and ensure all safe use conditions are met prior to dispensing bosentan to a patient, by using the same process as outpatient pharmacies.

What is a Pre-Dispense Authorization (PDA)?

A PDA is verification sent to outpatient and chain pharmacies by the Bosentan REMS, authorizing the pharmacy to dispense bosentan to an eligible patient. The following safe-use conditions are verified prior to every bosentan dispense:

- Prescriber is certified in the Bosentan REMS
- Patient is enrolled in the Bosentan REMS (for inpatient pharmacies, patient enrollment by their prescriber must occur prior to discharge)
- Pharmacy is certified in the Bosentan REMS
- Current completed liver testing for the patient is confirmed
  - If liver testing is not confirmed, the pharmacy can confirm with the patient or prescriber that the testing has been completed and enter this confirmation on the **Bosentan REMS Website** or call the Contact Center
- If the patient is a female of reproductive potential, a current completed pregnancy test for the patient is confirmed
  - If pregnancy testing is not confirmed, the pharmacy can confirm with the patient or prescriber that testing has been completed and enter this confirmation on the **Bosentan REMS Website** or call the Contact Center
- Current hepatotoxicity counseling for all patients, counseling for embryo-fetal toxicity for females of reproductive potential and pre-pubertal females, and the need to use reliable contraception for females of reproductive potential is confirmed
  - If counseling is not confirmed, the pharmacy can complete the counseling and confirm completion if counseling on the **Bosentan REMS Website** or by calling the Contact Center

How do I obtain a Pre-Dispense Authorization (PDA)?

Pharmacies can obtain a PDA by one of the following methods:

- Access the **Bosentan REMS Website** here
- Call the Contact Center at 1-866-359-2612

To verify the safe-use conditions in the Bosentan REMS, the certified outpatient and chain pharmacy must submit the following information:

- Patient First Name
- Patient Last Name
- Patient Date of Birth
- Patient Zip Code
- Prescriber Identifier (e.g., NPI)
- Date of Fill
- Days' Supply
- Quantity
- Product / NDC

Once a PDA is obtained, the outpatient and chain pharmacy can dispense bosentan to the patient.

Is an inpatient pharmacy required to obtain a Pre-Dispense Authorization (PDA)?

No, inpatient pharmacies are not required to obtain a PDA.

Inpatient pharmacies must dispense bosentan to patients only after calling the Contact Center at 1-866-359-2612, accessing the **Bosentan REMS Website** here, or accessing the patient's medical records to:

1. Verify that the patient is under the supervision and care of a prescriber who is certified
2. Verify that the patient is enrolled or will be enrolled in the Bosentan REMS prior to discharge
3. Verify counseling is complete
4. Verify liver testing and pregnancy testing (for females of reproductive potential) is complete

Authorized Representatives and enrolled pharmacy staff in an inpatient pharmacy can check inpatient REMS requirements from their dashboard on the **Bosentan REMS Website**. To check inpatient REMS requirements, the user enters the following data:

- Patient data: First Name, Last Name, Date of Birth, Zip Code (required)
- Prescription data: Date of Fill, Manufacturer, NDC-Number, Days Supply, Quantity (optional)
- Prescriber identifier: NPI

What activity may an outpatient or chain pharmacy perform if a Pre-Dispense Authorization (PDA) is not issued?

If a PDA is not issued because one or more of the safe-use conditions have not been met prior to dispensing bosentan, outpatient and chain pharmacies may perform the corresponding activity to address the reason that a PDA was not issued:

1. Contact the prescriber or the Bosentan REMS to indicate that the prescriber is not certified and must become certified in the Bosentan REMS before bosentan can be dispensed
2. Contact the prescriber or the Bosentan REMS to notify the prescriber that the patient is not enrolled and must be enrolled in the Bosentan REMS before bosentan can be dispensed
3. If a PDA is not issued because required testing is not confirmed, the outpatient pharmacy can confirm with the patient or prescriber that the testing has been completed and enter this confirmation in the **Bosentan REMS Website** or call the Contact Center

What happens when a patient tries to fill a prescription at a pharmacy that is not certified?

If a pharmacy is not certified in the Bosentan REMS, a patient will be unable to obtain bosentan at that pharmacy location, even if the patient meets other program element requirements as defined by the Bosentan REMS. Pharmacies must become certified in the Bosentan REMS in order to dispense bosentan to patients.

Will pharmacies that are not certified be able to order bosentan?

No, if a pharmacy is not certified in the Bosentan REMS, the pharmacy will not be approved to receive bosentan.

How will my wholesaler-distributor know whether the pharmacy is certified in the Bosentan REMS, so I can order bosentan?

Wholesalers-distributors must verify the pharmacy is certified in the Bosentan REMS prior to distributing bosentan to a pharmacy. Wholesalers-distributors may access the database of certified pharmacies provided by the Bosentan REMS, utilize the "Pharmacy Locator" on the **Bosentan REMS Website** or contact the Bosentan REMS for confirmation of pharmacy certification.

What if the authorized representative leaves the pharmacy?

If the authorized representative leaves the pharmacy, a new authorized representative must notify the Bosentan REMS of the change in the authorized representative by certifying in the Bosentan REMS.

Why do I need to verify the name and contact information for the authorized representative?

If, at any time, a pharmacy assigns a new authorized representative, the new authorized representative must certify in the Bosentan REMS. The name and contact information of the pharmacy's authorized representative must be verified every two years.

Who is considered pharmacy staff?

Any pharmacist or pharmacy employee in a certified pharmacy may assume the role of pharmacy staff to conduct basic program functions through the **Bosentan REMS Website** to be associated with a certified outpatient pharmacy.

What activities may a pharmacy staff member perform?

- Pharmacy staff in outpatient pharmacies will be able to request a PDA or receive a PDA
  - Pharmacy staff can confirm completion of liver testing and pregnancy testing (if applicable) on the **Bosentan REMS Website** or by calling the Contact Center
  - Pharmacy staff can complete counseling and confirm completion on the **Bosentan REMS Website** or by calling the Contact Center
- Pharmacy staff in inpatient pharmacies will be able to verify prescriber certification and patient enrollment

What is a refill dispense exception?

The Bosentan REMS allows prescribers to apply clinical judgment and authorize continued dispensing of bosentan to enrolled patients when a patient's testing could not be confirmed in a given month or for extended travel outside of the United States. In order for a pharmacy to dispense to a patient, the prescriber must authorize a refill dispense exception.

A refill dispense exception allows a prescriber to authorize a patient to receive up to a 30 days' supply of bosentan without confirmed pregnancy and/or liver testing. The refill dispense exception also allows the prescriber to authorize up to a 90 days' supply of bosentan for extended travel outside of the United States of more than 30 days.

In order for a patient to be eligible to receive a refill dispense exception due to testing not being confirmed in a given month:

- The patient must be enrolled in the Bosentan REMS
- The patient must have confirmed testing on file for the previous month
- The prescriber must attest that the benefits of receiving bosentan outweigh the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan

In order for a patient to be eligible to receive a refill dispense exception for extended travel outside of the United States:

- The patient must be enrolled in the Bosentan REMS
- The patient must have confirmed testing on file for the previous month
- The patient must be traveling outside of the United States for more than 30 days
- The prescriber must attest that the benefits of receiving bosentan outweigh the risks of hepatotoxicity and embryo-fetal toxicity associated with bosentan
- The prescriber must attest to continue to counsel the patient about the risk of embryo-fetal toxicity and hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity, and REMS requirements, including the need to complete liver testing and, as appropriate, pregnancy testing monthly while traveling outside of the United States
  - Test confirmation is not required to be provided to the Bosentan REMS while the patient is traveling outside of the United States

How does a prescriber authorize a refill dispense exception?

Only certified prescribers can authorize a refill dispense exception by:

- Calling the Contact Center at 1-866-359-2612
- Documenting the refill dispense exception authorization through the **Bosentan REMS Website**

Frequently Asked Questions (FAQs)

General | Prescriber | Pharmacy | Patient Management

Do patients need to be enrolled in the Bosentan REMS in order to receive bosentan?

Yes, any patient prescribed bosentan must be enrolled in the Bosentan REMS by the patient's prescriber. Patients in an inpatient setting must be enrolled in the Bosentan REMS prior to discharge.

How are patients enrolled in the Bosentan REMS?

Patients must be enrolled by their prescribers. Enrollment can be completed online here, by faxing the ***Patient Enrollment Form*** to the Contact Center at 1-800-730-8231, or by mailing it to the Bosentan REMS at 200 Pinecrest Plaza Morgantown, WV 26505. Patients or their parent/legal guardian must sign the ***Patient Enrollment Form*** online or on a hard copy of the form to complete the patient enrollment process.

How is Reproductive Potential Status defined for female patients?

Females of Reproductive Potential

- Females of reproductive potential include females who have entered puberty and all females who have a uterus and have not passed through menopause
- For the purposes of this REMS, puberty includes females who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)

Females of Non-Reproductive Potential

- Pre-pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
- Post-menopausal Females: Females who have passed through menopause. Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical form bilateral oophorectomy
- Females with other medical reasons for permanent, irreversible infertility

How are patient monthly tests and counseling reported to the Bosentan REMS?

Prescribers may report that the appropriate monthly tests, including liver tests for all patients, pregnancy test for females of reproductive potential, and appropriate counseling for all patients, have been completed by reporting it to the Bosentan REMS. This information can be reported by one of the following methods:

- Entering testing and counseling information online here
- Submitting a ***Testing and Patient Counseling Reporting Form*** by fax to the Bosentan REMS at 1-800-730-8231
- Calling the Contact Center at 1-866-359-2612

If monthly testing or counseling is not reported to the Bosentan REMS by the prescriber, the Contact Center or a certified pharmacy may confirm completion of the REMS requirements with the patient

What are the testing requirements for patients?

Liver tests are required for every patient and pregnancy tests are required for females of reproductive potential:

- Order and review liver tests for all patients:
  - Prior to initiating treatment
  - Monthly during treatment
- Order and review pregnancy tests for females of reproductive potential:
  - Prior to initiating treatment
  - Monthly during treatment
  - One month following treatment discontinuation

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Contact Us

If you have any questions or require additional information, please contact the Bosentan REMS.

Phone
1-866-359-2612

Fax
1-800-730-8231

Mailing Address
Bosentan REMS
200 Pinecrest Plaza
Morgantown, WV 26505

For additional information about the Bosentan REMS, please call 1-866-359-2612.

Bosentan
REMS Program

Prescribing Information | Medication Guide

Login

Prescribers | Pharmacies | Patients | Pharmacy Locator | FAQs

Prescribing Information and Medication Guides

Brand Name Products

Trade Name	Generic Name	Company	Contact	Medication Guide	Prescribing Information
				Medication Guide	Prescribing Information

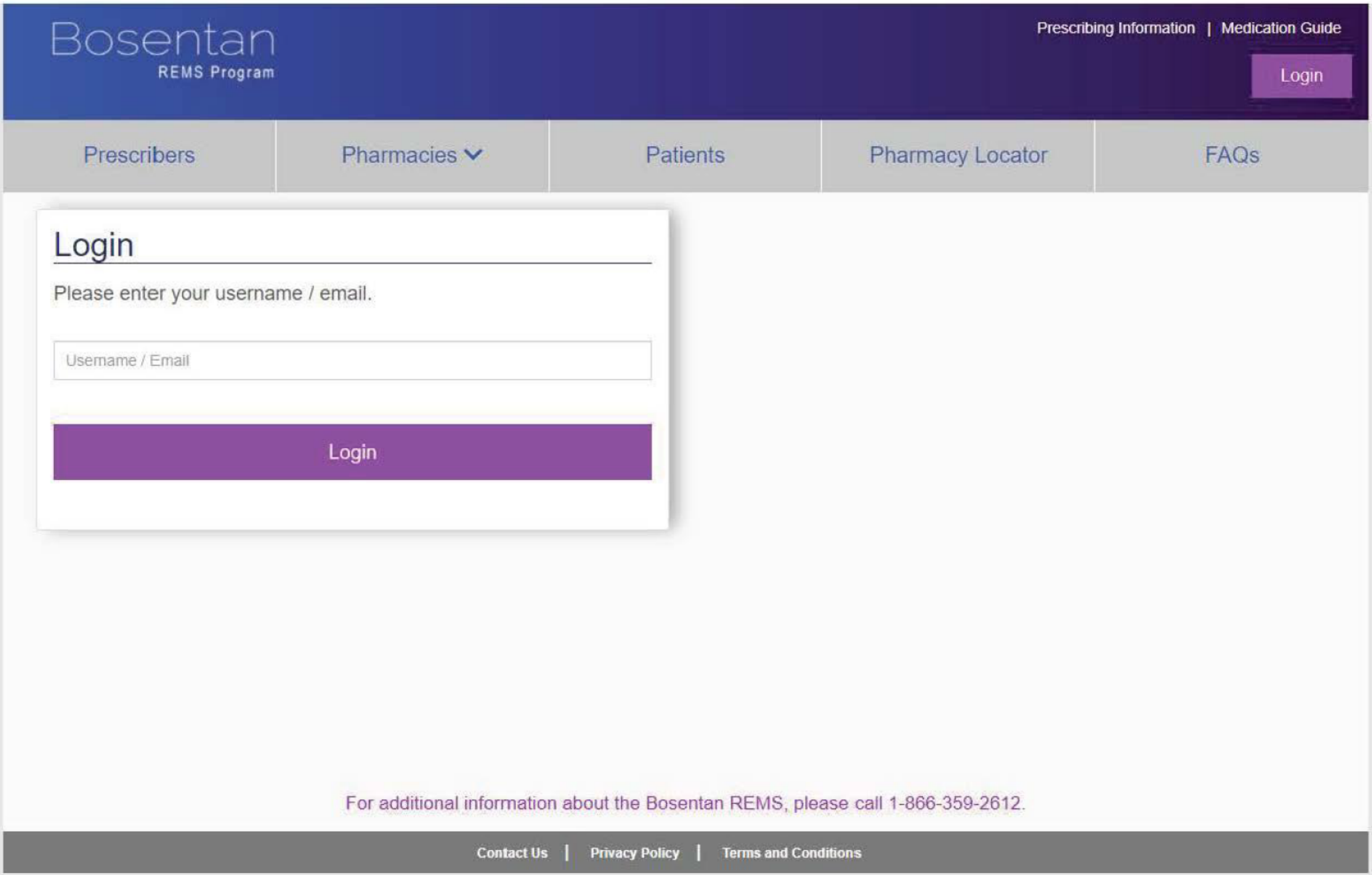
The Bosentan REMS Applicants attest that the table above will only include products listed in the link titled 'What medicines are included in the REMS' on the FDA Approved REMS website.

Generic Products

Generic Name	Company	Contact	Medication Guide	Prescribing Information
			Medication Guide	Prescribing Information

The Bosentan REMS Applicants attest that the table above will only include products listed in the link titled 'What medicines are included in the REMS' on the FDA Approved REMS website.

For additional information about the Bosentan REMS, please call 1-866-359-2612.


Bosentan
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Prescribing Information | Medication Guide
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Username / Email
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021290Orig1s043

OTHER REVIEW(S)

[redacted]

Office of Prescription Drug Promotion

Internal Consult

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Katherine Hyatt Hawkins Shaw, Health Communications Analyst, DRM

From: Charuni Shah, Regulatory Review Officer

CC: Charuni Shah, Regulatory Review Officer
Melinda Wilson, Team Leader
Deveonne Hamilton-Stokes, SRPM, OSE
Cynthia LaCavita, Team Leader, DRM
Till Olickal, Risk Management Analyst, DRM
Kate Heinrich Oswell, Health Communications Analyst, DRM
CDER-OPDP-RPM
Michael Wade

Date: March 17, 2022

Re: Comments on draft Risk Evaluation and Mitigation Strategies (REMS) Materials for shared Bosentan products (Submission date: March 4, 2022)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Bosentan:

- Healthcare Provider (HCP) REMS Materials:
  - Prescriber Fact Sheet
  - Prescriber Guide
  - Pharmacy Guide
  - Interactive Voice Response (IVR) System Flow and Recording Script
  - Prescriber Enrollment Form
  - Outpatient Pharmacy Enrollment Form

    - Inpatient Pharmacy Enrollment Form
    - Chain Pharmacy Headquarters Enrollment Form
    - Prescriber FAQs
    - Professional Society Letter
    - Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form
    - Prescriber Letter
    - Pharmacy Letter

- Direct-to-Consumer(DTC)(Patient) REMS Materials:
    - Patient Guide
    - Patient Enrollment Form

- HCP and DTC (Patient) REMS Materials:
    - Bosentan REMS Website

The version of the draft REMS materials used in this review were sent from Katherine Shaw, via email, on March 4, 2022. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Bosentan.

General Comments

Please remind the Bosentan applicants that REMS materials are not appropriate for use in a promotional manner.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comments below):

- Prescriber Fact Sheet
- Prescriber Guide
- Pharmacy Guide
- Interactive Voice Response (IVR) System Flow and Recording Script
- Prescriber Enrollment Form
- Outpatient Pharmacy Enrollment Form
- Inpatient Pharmacy Enrollment Form
- Chain Pharmacy Headquarters Enrollment Form
- Prescriber FAQs
- Professional Society Letter
- Change in Reproductive Potential Status and Pre-Pubertal Annual Verification Form
- Bosentan REMS Website

- Prescriber Letter
- Pharmacy Letter
- Patient Guide and Patient Enrollment Form

Specific Comment

We have no additional comments on these proposed materials at this time.
Thank you for your consult.

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/

CHARUNI P SHAH
03/17/2022 08:36:36 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021290Orig1s043

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

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

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

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

Dear Dr. Mazza:

We have received your supplemental new drug applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	021290 209279
SUPPLEMENT NUMBER:	043 009
PRODUCT NAME:	Tracleer (bosentan) Tablets Tracleer (bosentan) Tablets for Oral Suspension
DATE OF SUBMISSION:	November 4, 2021
DATE OF RECEIPT:	November 4, 2021

This supplemental application proposes the following modifications to the approved risk evaluation and mitigation strategy (REMS) for bosentan:

1. Update the REMS Document to the new format
2. Removal of the Bosentan REMS Pharmacy Network (Switch)
3. Addition of the Prescriber Designee role on the REMS website to allow prescribers to delegate certain administrative activities
4. Changes to the REMS website to allow certified pharmacies to enter testing and counseling information through the REMS website and allow pharmacists requesting a Pre-Dispense Authorization (PDA) to confirm counseling information

5. Changes to the pre-recorded messages in the Interactive Voice Response (IVR) System to align with the proposed modifications and new workflow

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 3, 2022, in accordance with 21 CFR: 314.101(a).

The goal date will be May 3, 2022.

If you have questions, call me at 301 796-3975.

Sincerely,

{See appended electronic signature page}

Lori Anne Wachter RN, BSN, RAC (US)
Regulatory Health Project Manager for Safety
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

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/

Lori A WACHTER
11/18/2021 08:10:47 AM