

# Bosentan

REMS Program

## Pharmacy Guide

# Table of Contents

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Table of Contents .....	2
About Bosentan .....	4
Risk of Hepatotoxicity .....	4
Bosentan REMS Overview .....	5
Bosentan REMS Pharmacy Types and Definitions .....	5
Authorized Representatives and Pharmacy Certification.....	6
Pre-Dispense Authorization (PDA) for Dispensing Bosentan for Outpatient Pharmacies.....	7
Steps for Outpatient Pharmacies .....	9
Steps for Chain Pharmacies.....	11
Steps for Inpatient Pharmacies .....	13

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 risk of hepatotoxicity, bosentan is only available through the Bosentan REMS.

This guide contains important information for pharmacies about the risk of hepatotoxicity associated with bosentan, 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**

# About Bosentan

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**Tracleer® and bosentan tablets for oral suspension** are 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 tablets** are indicated for the treatment of 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

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**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.

## Bosentan REMS Overview

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Due to the risk of hepatotoxicity, 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 risk of hepatotoxicity:

- Objective: Prescribers monitor patient’s liver enzymes monthly during treatment as described in the Prescribing Information

## Bosentan REMS Pharmacy Types and Definitions

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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:

<u>Pharmacy Type</u>	<u>Definition</u>
<b>Outpatient Pharmacy</b>	For the purposes of this REMS, outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.
<b>Chain Pharmacy</b>	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.
<b>Inpatient Pharmacy</b>	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

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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 REMS requirements
- 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 Applicants or a third party acting on behalf of the Applicants 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 9](#)

Specific duties of a **chain pharmacy** Authorized Representative are referenced on [page 11](#)

Specific duties of an **inpatient pharmacy** Authorized Representative are referenced on [page 13](#)

**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

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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 **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 **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
- 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 **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 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 risk of hepatotoxicity 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 risk of hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity, and REMS requirements including the need to complete liver 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

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The Authorized Representative for each outpatient pharmacy must complete the following steps in the Bosentan REMS:

1. **READ this guide to understand the risk of hepatotoxicity associated with bosentan and to learn about the Bosentan REMS**
  - The Authorized Representative for the pharmacy must understand the risk of hepatotoxicity associated with 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 risk of hepatotoxicity associated with 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 **REMS Website** at [www.BosentanREMSProgram.com](http://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 risk of hepatotoxicity 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 **REMS Website**
4. **DOCUMENT all staff training**
  - Certified pharmacies are subject to audit by the Applicants or a third party acting on behalf of the Applicants 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 **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 **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 **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. 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](http://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 **REMS Website**. The Contact Center can be reached at 1-866-359-2612.

# Steps for Chain Pharmacies

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The Authorized Representative for the chain pharmacy must complete the following steps in the Bosentan REMS:

- 1. READ this guide to understand the risk of hepatotoxicity associated with bosentan and to learn about the Bosentan REMS**
  - The Authorized Representative for the pharmacy must understand the risk of hepatotoxicity associated with 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 risk of hepatotoxicity associated with 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 **REMS Website** at [www.BosentanREMSProgram.com](http://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 risk of hepatotoxicity 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 **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 **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 Applicants or a third party acting on behalf of the Applicants 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 **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 **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 **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. 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](http://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 **REMS Website**. The Contact Center can be reached at 1-866-359-2612.

# Steps for Inpatient Pharmacies

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The Authorized Representative for each inpatient pharmacy must complete the following steps in the Bosentan REMS:

1. **READ this guide to understand the risk of hepatotoxicity associated with bosentan and to learn about the Bosentan REMS**
  - The Authorized Representative for the pharmacy must understand the risk of hepatotoxicity associated with 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 risk of hepatotoxicity associated with 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 **REMS Website** at [www.BosentanREMSProgram.com](http://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 **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 Applicants or a third party acting on behalf of the Applicants 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 **REMS Website**, or accessing the patient's medical record to verify:
    - The patient is under the care of a prescriber who is certified
    - The patient is enrolled or will be enrolled prior to discharge
    - The pharmacy is certified
    - Counseling on the risk of hepatotoxicity is complete

- Liver testing 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. **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](http://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 **REMS Website**. The Contact Center can be reached at 1-866-359-2612.

Please see the Prescribing Information for bosentan, including complete Boxed Warning for hepatotoxicity, and Medication Guides for each approved bosentan product, which can be found at [www.BosentanREMSProgram.com](http://www.BosentanREMSProgram.com).

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](http://www.BosentanREMSProgram.com).