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

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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 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**.