

Bosentan

REMS Program

Pharmacy Guide

The Bosentan **R**isk **E**valuation and **M**itigation **S**trategy (REMS) Program is a single shared 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 Program.

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 Program: Step by Step
- Inpatient Pharmacies' Role in the Bosentan REMS Program: Step by Step
- Counseling and Contraception for Females of Reproduction Potential

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About Bosentan

Tracleer® 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 damage. Liver function 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 ($>3 \times$ 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 after ending bosentan treatment. Patients must not become pregnant while taking bosentan.

What is the Bosentan REMS Program?

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 Program. The Bosentan REMS Program is a shared program including all brand and generic bosentan products.

The goal of the Bosentan REMS Program is to mitigate the risk 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 Program
 - 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 Program Pharmacy Types and Definitions

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

<u>Pharmacy Type</u>	<u>Definition</u>
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 Program.
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.

Definitions of Reproductive Potential Status

▪ Females of Reproductive Potential

- Females of reproductive potential include girls 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 girls 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**

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:

- Coordinates the activities required for the pharmacy and/or pharmacy staff in the Bosentan REMS Program
- Establishes and implements processes and procedures to ensure compliance with the safe use conditions of the Bosentan REMS Program
- Maintains documentation that all processes and procedures are in place and are being followed for the Bosentan REMS Program and provide upon request to the Bosentan Sponsors or a third party acting on behalf of the Bosentan Sponsors
- Complies with audits by the Bosentan Sponsors or a third party acting on behalf of the Bosentan Sponsors to ensure that all processes and procedures are in place and are being followed for the Bosentan REMS Program

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: Pharmacies must recertify in the Bosentan REMS Program if the pharmacy designates a new authorized representative.

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

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

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

- Patient is enrolled in the Bosentan REMS Program
- Prescriber is certified in the Bosentan REMS Program
- Current completed liver function test for the patient is confirmed
- If the patient is a female of reproductive potential, a current completed pregnancy test for the patient is confirmed
- Current hepatotoxicity counseling for the patient is confirmed
 - If counseling is not confirmed, call the Bosentan REMS Program Contact Center to complete the counseling requirement before dispensing bosentan
- Current embryo-fetal toxicity counseling for each female of reproductive potential is confirmed
 - If counseling is not confirmed, call the Bosentan REMS Program Contact Center to receive complete the counseling requirement before dispensing bosentan

To verify the safe use conditions in the Bosentan REMS Program, 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. DEA or 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.

- If your outpatient pharmacy supports electronic telecommunication verification with the Bosentan REMS Program system, your pharmacy must process reverse the PDA through your pharmacy management system
- If your outpatient pharmacy does NOT support electronic telecommunication verification with the Bosentan REMS Program system, your pharmacy must reverse the PDA by calling the Bosentan REMS Program Contact Center or accessing the ***Bosentan REMS Program 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-day supply of bosentan without confirmed pregnancy and/or liver function testing, or up to a 90-day 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 risk of embryo-fetal toxicity and hepatotoxicity associated with bosentan, the signs and symptoms of hepatotoxicity, and program requirements including the need to complete liver function 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 Program from the prescriber.

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

Outpatient Pharmacies' Role in the Bosentan REMS Program: Step by Step

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

1. **READ the Prescribing Information for bosentan and Medication Guide and this guide to understand the risks of bosentan and to learn about the Bosentan REMS Program**
 - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS Program, prior to certifying their pharmacy
2. **ENROLL the pharmacy by completing the *Bosentan REMS Program 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 Program as described in the *Bosentan REMS Program Outpatient Pharmacy Enrollment Form*
 - The authorized representative can complete the enrollment form online or download paper copies from the *Bosentan REMS Program Website* at www.BosentanREMSProgram.com and fax the form to the Bosentan REMS Program at 1-800-730-8231
 - If your outpatient pharmacy supports electronic telecommunication verification with the Bosentan REMS Program system, during the enrollment process your authorized representative will be instructed to verify the PDA is operational using established telecommunication standards, and by running the standardized validation test transactions to validate the system enhancements
3. **TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS Program 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 Program as defined in the *Bosentan REMS Program Outpatient Pharmacy Enrollment Form*
 - Any pharmacy employee may assume the role of pharmacy staff and associate with a certified outpatient pharmacy by accessing the *Bosentan REMS Program Website*
 - Pharmacy staff in outpatient pharmacies that do NOT support electronic communication verification with the Bosentan REMS Program system will be able to request a PDA
4. **DOCUMENT all staff training**
 - Certified pharmacies are subject to audit by Bosentan Sponsors or a third party acting on behalf of Bosentan Sponsors to ensure that all processes and procedures are in place and are being followed for the Bosentan REMS Program
5. **VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan**
 - Outpatient pharmacies must obtain a PDA prior to dispensing bosentan to a patient
 - If your outpatient pharmacy supports electronic telecommunication verification with the Bosentan REMS Program system, your pharmacy must dispense bosentan to patients only after obtaining a PDA through your pharmacy management system
 - If your outpatient pharmacy does NOT support electronic telecommunication verification with the Bosentan REMS Program system, your pharmacy must dispense bosentan to patients only after obtaining a PDA by calling the Bosentan REMS Program Contact Center or accessing the *Bosentan REMS Program 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:
 - Certify the pharmacy in the Bosentan REMS Program
 - Contact the prescriber or the Bosentan REMS Program to notify the prescriber that certification is required in the Bosentan REMS Program before bosentan can be dispensed
 - Contact the prescriber or the Bosentan REMS Program to notify the prescriber that the patient must be enrolled in the Bosentan REMS Program before bosentan can be dispensed
 - If a PDA is not issued because required testing is not confirmed, the outpatient pharmacy can call the Bosentan REMS Program Contact Center at 1-866-359-2612 to confirm with the patient or the patient's prescriber that the testing has been completed before bosentan can be dispensed
 - If counseling is not confirmed in the Bosentan REMS Program, a PDA will be issued if all other safe use conditions are met. The pharmacy must call the Bosentan REMS Program Contact Center to complete the counseling requirement before bosentan is dispensed. The Contact Center will provide counseling guidelines to the pharmacy. The pharmacy is required to counsel the patient according to the guidelines from the Contact Center
 - The Contact Center agents will be available during normal business hours. The Contact Center agent will provide the counseling guidelines and document the counseling
 - An interactive voice response system will be available 24/7. The system will provide the counseling guidelines and document the counseling
6. **DISPENSE up to a 30-day supply, along with a copy of the Medication Guide for the bosentan product that is dispensed**
- Up to a 90-day 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. **NOT TRANSFER BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS Program**
8. **NOTIFY the Bosentan REMS Program of all adverse events including those suggestive of hepatotoxicity**
9. **REPORT any pregnancy and all available information during treatment with bosentan to the Bosentan REMS Program**

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

Chain Pharmacies' Role in the Bosentan REMS Program: Step by Step

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

1. **READ the Prescribing information for bosentan and Medication Guide and this guide to understand the risks of bosentan and to learn about the Bosentan REMS Program**
 - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS Program, prior to certifying their pharmacy
2. **ENROLL the chain pharmacy by completing the *Bosentan REMS Program 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 Program as described in the *Bosentan REMS Program Chain Pharmacy Headquarters Enrollment Form*
 - The authorized representative can complete the enrollment form online or download paper copies from the *Bosentan REMS Program Website* at www.BosentanREMSProgram.com and fax the form to the Bosentan REMS Program at 1-800-730-8231
 - Ensure the pharmacy enables its pharmacy management system to support communication with the Bosentan REMS Program system, using established telecommunication standards, and runs the standardized validation test transactions to validate the system enhancements
3. **TRAIN all pharmacy staff who participate in dispensing bosentan on the Bosentan REMS Program 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 Program as defined in the *Bosentan REMS Program Chain Pharmacy Headquarters Enrollment Form*
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 Program online through www.BosentanREMSProgram.com, or by contacting the Bosentan REMS Program Contact Center at 1-866-359-2612 to obtain instructions on providing a list of trained pharmacy locations. Once the Bosentan REMS Program confirms the required dispensing information, the dispensing location will be authorized to purchase, receive, and dispense bosentan
 - Certified pharmacies are subject to audit by Bosentan Sponsors or a third party designated by Bosentan Sponsors to ensure that all processes and procedures are in place and are being followed for the Bosentan REMS Program
5. **VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan**
 - Chain pharmacies must dispense bosentan to patients only after obtaining a pre-dispense authorization (PDA) by processing the prescription, including cash claims, through their pharmacy management system
 - 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:
 - Certify the pharmacy in the Bosentan REMS Program
 - Contact the prescriber or the Bosentan REMS Program to notify the prescriber that certification is required in the Bosentan REMS Program before bosentan can be dispensed
 - Contact the prescriber or the Bosentan REMS Program to notify the prescriber that the patient must be

enrolled in the Bosentan REMS Program before bosentan can be dispensed

- If a PDA is not issued because required testing is not confirmed, the pharmacy can call the Bosentan REMS Program Contact Center at 1-866-359-2612 to confirm with the patient or the patient's prescriber that the testing has been completed before bosentan can be dispensed
 - If counseling is not confirmed in the Bosentan REMS Program, a PDA will be issued if all other safe use conditions are met. The pharmacy must call the Bosentan REMS Program Contact Center to complete the counseling requirement before bosentan is dispensed. The Contact Center will provide counseling guidelines to the pharmacy. The pharmacy is required to counsel the patient according to the guidelines from the Contact Center
 - The Contact Center agents will be available during normal business hours. The Contact Center agent will provide the counseling guidelines and document the counseling
 - An interactive voice response system will be available 24/7. The system will provide the counseling guidelines and document the counseling
6. **DISPENSE up to a 30-day supply, along with a copy of the Medication Guide for the bosentan product that is dispensed**
- Up to a 90-day 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. **NOT TRANSFER BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS Program**
8. **NOTIFY the Bosentan REMS Program of all adverse events including those suggestive of hepatotoxicity**
9. **REPORT any pregnancy and all available information during treatment with bosentan to the Bosentan REMS Program**

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

Inpatient Pharmacies' Role in the Bosentan REMS Program: Step by Step

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

- 1. READ the Prescribing information for bosentan and Medication Guide and this guide to understand the risks of bosentan and to learn about the Bosentan REMS Program**
 - The authorized representative for the pharmacy must understand the risks of bosentan and become familiar with the Bosentan REMS Program, prior to enrolling their pharmacy
- 2. ENROLL the pharmacy by completing the *Bosentan REMS Program 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 Program as described in the *Bosentan REMS Program Inpatient Pharmacy Enrollment Form*
 - The authorized representative can complete the enrollment form online or download paper copies from the *Bosentan REMS Program Website* at www.BosentanREMSProgram.com and fax the form to the Bosentan REMS Program at 1-800-730-8231
- 3. TRAIN all dispensing staff on the Bosentan REMS Program**
 - Prior to dispensing bosentan, the authorized representative must ensure that all staff are appropriately trained on the Bosentan REMS Program procedures and materials as defined in the *Bosentan REMS Program Inpatient Pharmacy Enrollment Form*
 - Any pharmacy employee may assume the role of a pharmacy staff member and associate with a certified inpatient pharmacy by accessing the *Bosentan REMS Program 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 Bosentan Sponsors or a third party designated by Bosentan Sponsors to ensure that all processes and procedures are in place and are being followed for the Bosentan REMS Program
- 5. VERIFY SAFE USE CONDITIONS for each patient prior to dispensing bosentan**
 - Dispense bosentan to patients only after calling the Bosentan REMS Contact Center, accessing the *Bosentan REMS Program 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
- 6. DISPENSE no more than a 15-day supply of bosentan upon discharge**
- 7. NOT TRANSFER BOSENTAN to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS Program**
- 8. NOTIFY the Bosentan REMS Program of all adverse events including those suggestive of hepatotoxicity**
- 9. REPORT any pregnancy and all available information during treatment with bosentan to the Bosentan REMS Program**

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

Counseling and Contraception for Females of Reproductive Potential

All females of reproductive potential must use reliable contraception during treatment with bosentan and for one month after ending bosentan treatment. 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 ***Bosentan REMS Program 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
<p>One method from this list:</p> <p>Standard intrauterine device (Copper T 380A IUD)</p> <p>Intrauterine system (LNg 20 IUS; progesterone IUS)</p> <p>Tubal sterilization</p>	<p>One method from this list:</p> <p>Estrogen and progesterone oral contraceptives ("the pill")</p> <p>Estrogen and progesterone transdermal patch</p> <p>Vaginal ring</p> <p>Progesterone injection</p> <p>Progesterone implant</p> <p>PLUS</p> <p>One Method from this list:</p> <p>Male condom</p> <p>Diaphragm with spermicide</p> <p>Cervical cap with spermicide</p>	<p>One method from this list:</p> <p>Diaphragm with spermicide</p> <p>Cervical cap with spermicide</p> <p>PLUS</p> <p>One Method from this list:</p> <p>Male condom</p>	<p>One method from this list:</p> <p>Partner's vasectomy</p> <p>PLUS</p> <p>One Method from this list:</p> <p>Male condom</p> <p>Diaphragm with spermicide</p> <p>Cervical cap with spermicide</p> <p>Estrogen and progesterone oral contraceptives ("the pill")</p> <p>Estrogen and progesterone transdermal patch</p> <p>Vaginal ring</p> <p>Progesterone injection</p> <p>Progesterone implant</p>

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

Notify the Bosentan REMS Program of all adverse events, including those suggestive of hepatotoxicity, during treatment with bosentan. Notify the Bosentan REMS Program of any pregnancy and all available information during treatment with bosentan.