

Bosentan

REMS Program

Prescriber 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 prescribers about the risks of Bosentan, including hepatotoxicity and embryo-fetal toxicity, and includes:

- Bosentan REMS Program Overview
- Overview of Enrollment Requirements for Prescribers
- Bosentan Liver Function Treatment Results and Monitoring Recommendations
- Prescriber's Role in the Bosentan REMS Program: Step by Step
- Contraception Options for Females of Reproductive 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.

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- 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 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 Function 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 ($>3 \times \text{ULN}$) **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 Risk Evaluation and Mitigation Strategy (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 Overview

- All healthcare providers must certify in the Bosentan REMS Program and comply with the Bosentan REMS Program requirements in order to prescribe a bosentan product
- All patients must be enrolled in the Bosentan REMS Program. Enrolled patients must comply with the Bosentan REMS Program requirements in order to receive bosentan:
 - Patients must agree to complete liver function tests, and pregnancy tests as appropriate for the patient’s reproductive potential classification prior to receiving bosentan
 - All patients must agree to be counseled on the Bosentan REMS Program and the risks of treatment with bosentan
 - All patients must agree to be contacted about completing required monthly testing and counseling
- **For all patients:**
 - Prescribers must counsel all patients on the risk of 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 by reviewing and providing the ***Bosentan REMS Program Guide for Patients*** to each patient
 - Prescribers must complete the ***Bosentan REMS Program Patient Enrollment Form*** with every bosentan patient and submit the form to the Bosentan REMS Program prior to initiating treatment
 - Counsel patients who fail to comply with program requirements
 - Prescribers must order and review liver function tests results before bosentan treatment initiation
 - Prescribers must order and review monthly liver function tests
 - Prescribers must report all adverse events including those suggestive of hepatotoxicity to the Bosentan REMS Program
- **For all female patients:**
 - Prescribers must determine the reproductive potential status of every female before initiating bosentan treatment as defined on [Page 7](#) of this guide
 - Prescribers must report a change or misclassification in reproductive potential status by submitting a ***Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*** to the Bosentan REMS Program within 10 business days of becoming aware of the change
 - Prescribers must report any pregnancy and all available information during treatment with bosentan to the Bosentan REMS Program
- **For females of reproductive potential:**
 - Prescribers must counsel patients about the risk of embryo-fetal toxicity and the need to use reliable contraception prior to initiating treatment, during bosentan treatment, and for one month after ending treatment
 - Prescribers must counsel the patient to immediately contact her healthcare provider if she misses a menstrual period or suspects pregnancy
 - Prescribers must order and review pregnancy tests prior to initiation of bosentan treatment, monthly during treatment, and for one month after ending treatment
- **For pre-pubertal female patients:**
 - Prescribers must counsel the patient and/or a parent/legal guardian about the risk of embryo-fetal toxicity

- Prescribers must counsel the patient and/or a parent/legal guardian to immediately contact her healthcare provider if she begins to menstruate
 - Prescribers must evaluate patients age 8 years and older¹ at least annually for any change in reproductive status and submit a **Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form** to the Bosentan REMS Program within 10 business days of becoming aware of the change
 - Prescribers may report that the appropriate monthly tests and counseling, comprising liver function tests (for all patients), pregnancy tests for females of reproductive potential, and monthly counseling have been completed by reporting it to the Bosentan REMS Program. This information can be reported by one of the following methods:
 - Submitting a **Bosentan REMS Program Testing and Patient Counseling Reporting Form** by fax to the Bosentan REMS Program at 1-800-730-8231
 - Completing the **Bosentan REMS Program Testing and Patient Counseling Reporting Form** online at **www.BosentanREMSProgram.com**
 - Calling the Bosentan REMS Program at 1-866-359-2612
- Note: Use of the **Bosentan REMS Program Testing and Patient Counseling Reporting Form** is voluntary.
- 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 Program can dispense bosentan

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**

¹ Clinical threshold for evaluating onset of puberty.

Overview of 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 Program	X			
Prescriber counsels the patient using the <i>Bosentan REMS Program Guide for Patients</i> , particularly on the risks of hepatotoxicity and embryo-fetal toxicity and the need to use reliable contraception	X*			
Prescriber must order and review liver function tests prior to initiation of treatment and monthly during treatment	X			
Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for one month after ending treatment		X		
Prescriber must verify reproductive status annually in patients 8 years of age or older by completing the <i>Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form</i>			X	
Prescriber must complete the <i>Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form</i> 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 and/or a parent/legal guardian: Counsel only about the risks of hepatotoxicity, embryo-fetal toxicity and the need to immediately contact the prescriber if the patient begins to menstruate.

Tracleer® and Bosentan Liver Function 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 function test results. Elevated monthly liver function 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	<p>Confirm by another aminotransferase test: if confirmed:</p> <ul style="list-style-type: none"> ▪ <u>in adults and pediatric patients >12 years and >40 kg</u>, 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. ▪ <u>in all other pediatric patients*</u>, 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	<p>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,</p> <ul style="list-style-type: none"> ▪ <u>in adults and pediatric patients >12 years and >40 kg</u>, consider reintroduction of treatment at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. ▪ <u>in all other pediatric patients*</u>, consider reintroduction at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
>8 x ULN	<p>Stop treatment permanently. There is no experience with reintroduction of Tracleer in these circumstances.</p>

*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	<p>Confirm by another aminotransferase test; if confirmed,</p> <ul style="list-style-type: none"> • <u>in patients >12 years and >40 kg</u>, 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. • <u>in patients > 12 years and <40 kg</u>, 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	<p>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,</p> <ul style="list-style-type: none"> • <u>in patients >12 years</u>, consider reintroduction of the treatment of 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days.
> 8 x ULN	<p>Stop treatment permanently. There is no experience with reintroduction of bosentan in these circumstances.</p>

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

What is a Refill Dispense Exception?

The Bosentan REMS Program 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 confirmed pregnancy and/or liver function 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 Program
- 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 Program
- 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 program requirements including the need to complete liver function 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 Program while the patient is traveling outside of the United States

Only certified prescribers can authorize a refill dispense exception by:

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

Prescriber's Role in the Bosentan REMS Program: Step by Step

Prescribers must complete the following steps in the Bosentan REMS Program:

1. **READ** the Prescribing Information for bosentan and Medication Guide for the prescribed product and this guide to understand the risks of bosentan and to learn about the Bosentan REMS Program
 - You must understand the risks of bosentan and become familiar with the Bosentan REMS Program
2. **COMPLETE** a *Bosentan REMS Program 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 Program
 - You can complete the *Bosentan REMS Program Prescriber 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. **DETERMINE** the reproductive potential status for female patients
 - You should identify female patients (captured on the *Bosentan REMS Program Patient Enrollment Form*) as one of the following categories:
 - **Female of Reproductive Potential**
 - **Female of Non-Reproductive Potential** (choose one of the options below)
 - Pre-pubertal female of non-reproductive potential
 - Post-menopausal female of non-reproductive potential
 - Female with other medical reasons for permanent, irreversible infertility
 - Expanded definitions are provided in the section above: "[Bosentan REMS Program Overview](#)"
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 program requirements including the need to complete liver function testing and, as appropriate, pregnancy testing by reviewing and providing the *Bosentan REMS Program Guide for Patients* to each patient
 - Complete the *Bosentan REMS Program Patient Enrollment Form* with every bosentan patient and submit the form to the Bosentan REMS Program prior to initiating treatment
 - Educate patients about the Bosentan REMS Program
 - Order and review pretreatment liver function tests
 - Order and review monthly liver function tests
 - Notify the Bosentan REMS Program of all adverse events including those suggestive of hepatotoxicity
 - Notify the Bosentan REMS Program of any pregnancy and all available information during treatment with bosentan

- 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 prior to initiating treatment, during bosentan treatment, and for one month after ending treatment
 - Counsel the patient to immediately contact her healthcare provider if she misses a menstrual period or suspects pregnancy
 - Order and review pregnancy tests prior to initiation of bosentan treatment, monthly during treatment, and for one month after ending treatment
- For pre-pubertal females, you must:
 - Counsel the patient and/or a parent/legal guardian about the risk of embryo-fetal toxicity
 - Counsel the patient and/or a parent/legal guardian to immediately contact her healthcare provider if she begins to menstruate
 - Evaluate patients age 8 years and older at least annually for any change in reproductive status and submit a ***Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*** to the Bosentan REMS Program within 10 business days of becoming aware of the change

5. ENROLL all patients in the Bosentan REMS Program by ensuring patients complete the *Bosentan REMS Program Patient Enrollment Form*

- Confirm the patient has agreed to comply with program requirements and has signed the form where indicated
- Fax the completed form to the Bosentan REMS Program at 1-800-730-8231, or complete the form online at **www.BosentanREMSProgram.com**
- Keep the original form with the patient’s records

6. TEST each patient’s liver function and pregnancy status of females of reproductive potential

- Order and review liver function 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 after ending bosentan treatment

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

- **For all patients:**
 - Order and review liver function tests each month during treatment with bosentan
 - Prescribers may, though are not required to, confirm the completion of liver function tests and counseling each month by one of the following methods:
 - Submitting a ***Bosentan REMS Program Testing and Patient Counseling Reporting Form*** by fax to the Bosentan REMS Program at 1-800-730-8231
 - Completing the ***Bosentan REMS Program Testing and Patient Counseling Reporting Form*** online at **www.BosentanREMSProgram.com**
 - Calling the Bosentan REMS Program 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 $\geq 2 \times$ ULN

- **For all females of reproductive potential:**
 - Order and review pregnancy tests monthly during treatment with bosentan and for one month after ending treatment
 - You may, though you are not required to, confirm the completion of pregnancy tests and counseling each month by one of the following methods:
 - Submitting a **Bosentan REMS Program Testing and Patient Counseling Reporting Form** by fax to the Bosentan REMS Program at 1-800-730-8231
 - Completing the **Bosentan REMS Program Testing and Patient Counseling Reporting Form** online at **www.BosentanREMSProgram.com**
 - Calling the Bosentan REMS Program at 1-866-359-2612
 - Report any pregnancy and all available information during treatment with bosentan to the Bosentan REMS Program
 - Monitor patient’s reproductive status during treatment with bosentan and report any change or misclassification in reproductive potential status by submitting a **Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form** to the Bosentan REMS Program within 10 business days of becoming aware of the change

- **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 **Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form** to the Bosentan REMS Program within 10 business days of becoming aware of the change
 - For each patient who is 8 years of age or older, verify annually and report the reproductive status by completing and submitting the **Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form** to the Bosentan REMS Program within 10 business days of becoming aware of the change

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.

Important Information for Prescribers of 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 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 Program at 1-866-359-2612 of any pregnancies that occur during treatment or within one month of ending bosentan treatment

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

Bosentan

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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 the Medication Guide 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. Notify the Bosentan REMS Program of any pregnancy and all available information during treatment with bosentan.