BACKGROUND

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

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

Prescribers must be certified in the Bosentan REMS.

Pharmacies must be certified in the Bosentan REMS.

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

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

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

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

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

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

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

At all times, I must:

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

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

Before treatment, I must:

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

During treatment, before each prescription, I must:

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

At all times, I must:

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

MALES

Before treatment, I must:

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

During treatment, before each prescription, I must:

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

At all times, I must:

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

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

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

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

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

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