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RISK EVALUATION AND MITIGATION STRATEGY (REMS) Bosentan REMS

A. Single Shared System for Bosentan

I. Goals

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

II. Elements to Assure Safe Use

1. Healthcare providers who prescribe bosentan must be certified

- a. To become certified to prescribe bosentan, prescribers must:
 - i. Review the Prescribing Information for bosentan
 - ii. Review the *Bosentan REMS Program Prescriber Guide*
 - iii. Enroll in the Bosentan REMS Program by completing the *Bosentan REMS Program Prescriber Enrollment Form* and submitting it to the Bosentan REMS Program

- b. As a condition of certification, prescribers must:
- i. Enroll each patient in the Bosentan REMS Program by performing the following:
 - 1) Counsel the patient about 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*
 - 2) Determine the reproductive potential status of each female patient as defined in the *Bosentan REMS Program Prescriber Guide*
 - 3) For pre-pubertal females, counsel the patient and/or parent/legal guardian about (i) the risk of embryo-fetal toxicity, (ii) the need to immediately contact the prescriber if the patient begins to menstruate
 - 4) For females of reproductive potential, counsel the patient about (i) the risk of embryo-fetal toxicity, (ii) the need to use reliable contraception as defined in the *Bosentan REMS Program Prescriber Guide* during treatment and for one month following treatment discontinuation, (iii) the need to immediately contact her prescriber if she misses a menstrual period or suspects she is pregnant, and (iv) her medical options in the event of unprotected sexual intercourse or known or suspected contraception failure
 - 5) Complete the *Bosentan REMS Program Patient Enrollment Form* for each patient and provide a completed copy to the patient. Submit the completed form to the REMS Program
 - ii. Report all adverse events including those suggestive of hepatotoxicity to the Bosentan REMS Program
 - iii. Report any pregnancy and all available information during treatment with bosentan to the Bosentan REMS Program
 - iv. Report a change or misclassification in the reproductive status of any female patient by completing the *Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
 - v. Perform the following requirements on an ongoing basis for each patient:
 - 1) Order and review liver function test results before bosentan treatment initiation and monthly during treatment

- 2) Counsel patients who fail to comply with program requirements
- vi. Perform the following monitoring on an ongoing basis for each pre-pubertal female:
 - 1) Evaluate patients age 8 years and older at least annually for any change in reproductive status and complete the *Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* verifying their reproductive potential status
- vii. Perform the following monitoring on an ongoing basis for each female patient of reproductive potential:
 - 1) Order and review pregnancy test results before bosentan treatment initiation, monthly during treatment, and for one month following treatment discontinuation
- c. Bosentan Sponsors must:
 - i. Ensure that healthcare providers who prescribe bosentan are certified, in accordance with the requirements described above
 - ii. Provide all the following mechanisms for healthcare providers to complete the certification process for the Bosentan REMS Program: online, mail, fax
 - iii. Ensure that healthcare providers are notified when they have been certified by the Bosentan REMS Program
 - iv. Maintain a validated, secure database of healthcare providers who are certified to prescribe bosentan in the Bosentan REMS Program. The database must link the prescribers' information and date of certification to their enrolled patients' information and update it accordingly
 - v. Ensure that healthcare providers meet the REMS requirements and decertify healthcare providers who do not maintain compliance with REMS requirements
 - vi. Ensure that certified prescribers are provided access to the database of certified pharmacies and enrolled patients
 - vii. Provide the *Bosentan REMS Program Prescriber Enrollment Form*, *Bosentan REMS Program Prescriber Guide*, *Bosentan REMS Program Fact Sheet*, *Bosentan REMS Program Patient Enrollment Form*, *Bosentan REMS Program Guide for Patients*, and *Bosentan REMS Program Testing and Patient Counseling Reporting Form* to healthcare providers who (1) attempt to prescribe bosentan and are not yet certified, or (2) inquire about how to become certified

The following materials are part of the REMS and are appended:

- *Bosentan REMS Program Prescriber Guide*
- *Bosentan REMS Program Prescriber Enrollment Form*
- *Bosentan REMS Program Guide for Patients*
- *Bosentan REMS Program Patient Enrollment Form*
- *Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- *Bosentan REMS Program Fact Sheet*
- *Bosentan REMS Program Testing and Patient Counseling Reporting Form*
- *Bosentan REMS Program Website* (www.BosentanREMSProgram.com)

2. Pharmacies that dispense bosentan must be certified

- a. To become certified to dispense bosentan, pharmacies must:
 - i. Designate an authorized representative to complete the certification process by submitting the appropriate completed form on behalf of the pharmacy:
 - 1) *Bosentan REMS Program Outpatient Pharmacy Enrollment Form*¹
 - 2) *Bosentan REMS Program Chain Pharmacy Headquarters Enrollment Form*²
 - 3) *Bosentan REMS Program Inpatient Pharmacy Enrollment Form*³
 - ii. Ensure that the authorized representative oversees the implementation of and compliance with the Bosentan REMS Program requirements by the following:
 - 1) Review the *Bosentan REMS Program Pharmacy Guide*

¹ For the purposes of this REMS outpatient pharmacies include but are not limited to retail, specialty, mail order, and closed system pharmacies.

² 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.

³ For the purposes of this REMS inpatient pharmacies include but are not limited to pharmacies in hospitals, hospices, long-term care facilities, and prisons.

- 2) Ensure all relevant staff involved in the dispensing of bosentan are trained on the Bosentan REMS Program requirements as described in the *Bosentan REMS Program Pharmacy Guide* and maintain a record of the training
- b. As a condition of certification:
- i. Pharmacies must recertify in the Bosentan REMS Program if the pharmacy designates a new authorized representative
 - ii. Report all adverse events including those suggestive of hepatotoxicity to the Bosentan REMS Program
 - iii. Report any pregnancy and all available information during treatment with bosentan to the Bosentan REMS Program
 - iv. Maintain 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
 - v. Comply 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
 - vi. Outpatient Pharmacies:
 - 1) Put processes and procedures in place to ensure the following requirements are completed prior to dispensing bosentan
 - a) Obtain a pre-dispense authorization from the Bosentan REMS Program by accessing the *Bosentan REMS Program Website*, calling the Bosentan REMS Program Contact Center, or enabling the pharmacy management system to support communication with the Bosentan REMS Program
 - 2) That support electronic telecommunication verification with the Bosentan REMS Program system must:
 - a) 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
 - b) Dispense bosentan to patients only after obtaining pre-dispense authorization by processing prescriptions, including cash claims, through their pharmacy management system to electronically:

- i) Verify the prescriber is certified and the patient is enrolled
 - ii) Verify the patient has completed the liver function tests and each female of reproductive potential has completed the pregnancy test or the prescriber has authorized a refill for patients if testing could not be confirmed
 - iii) Verify if the patient has been counseled on the risk of hepatotoxicity and each female of reproductive potential has been counseled on the risk of embryo-fetal toxicity and the need to use reliable contraception
- c) If counseling was not completed, call the Bosentan REMS Program Contact Center to complete the counseling requirement before dispensing bosentan
- d) Dispense up to a 30-day supply of bosentan
- e) Not transfer bosentan to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS Program
- 3) That do NOT support electronic telecommunication verification with the Bosentan REMS Program system must:
- a) Dispense bosentan to patients only after obtaining a pre-dispense authorization by calling the Bosentan REMS Program Contact Center or accessing the *[Bosentan REMS Program Website](#)* to:
 - i) Verify the prescriber is certified, and the patient is enrolled
 - ii) Verify the patient has completed the liver function tests and each female of reproductive potential has completed the pregnancy test, or the prescriber has authorized a refill for patients if testing could not be confirmed
 - iii) Verify if the patient has been counseled on the risk of hepatotoxicity and each female of reproductive potential has been counseled on the risk of embryo-fetal toxicity and the need to use reliable contraception
 - b) If counseling was not completed, call the Bosentan REMS Program Contact Center to complete the counseling requirement before dispensing bosentan
 - c) Dispense up to a 30-day supply of bosentan

- d) Not transfer bosentan to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS Program

vii. Inpatient Pharmacies:

- 1) Put processes and procedures in place to ensure the following requirements are completed prior to dispensing bosentan:
 - a) Verify the patient is under the supervision and care of a prescriber who is certified
 - b) Verify the patient is enrolled or will be enrolled prior to discharge
 - c) Verify the patient has completed the liver function tests and each female of reproductive potential has completed the pregnancy test
 - d) Verify if the patient has been counseled on the risk of hepatotoxicity and each female of reproductive potential has been counseled on the risk of embryo-fetal toxicity and the need to use reliable contraception
 - e) Dispense no more than a 15-day supply of bosentan upon discharge
- 2) Verify the requirements by the following mechanisms, including but not limited to calling the Bosentan REMS Program Contact Center, accessing the [*Bosentan REMS Program Website*](#), or by accessing the patient's medical records
- 3) Not transfer bosentan to any pharmacy, practitioner, or any healthcare setting not certified in the Bosentan REMS Program

c. Bosentan Sponsors must:

- i. Ensure that pharmacies that dispense bosentan are certified, in accordance with the requirements described above
- ii. Provide all the following mechanisms for pharmacies to complete certification for the Bosentan REMS Program: online, mail, fax
- iii. Ensure that pharmacies are notified when they have been certified by the Bosentan REMS Program
- iv. Ensure that certified pharmacies are provided access to the database of certified prescribers and enrolled patients
- v. Verify every 2 years that the authorized representative's name and contact information correspond to those of the current designated authorized

representative for the certified pharmacy. If different, the pharmacy must be required to recertify with a new authorized representative

The following materials are part of the REMS and are appended:

- *Bosentan REMS Program Outpatient Pharmacy Enrollment Form*
- *Bosentan REMS Program Chain Pharmacy Headquarters Enrollment Form*
- *Bosentan REMS Program Inpatient Pharmacy Enrollment Form*
- *Bosentan REMS Program Pharmacy Guide*

3. Bosentan must be dispensed with evidence or other documentation of safe use conditions

- a. To become enrolled in the Bosentan REMS Program, the patient and/or parent/legal guardian must sign a *Bosentan REMS Program Patient Enrollment Form* indicating that he/she has:
 - i. Received and has read the *Bosentan REMS Program Guide for Patients*
 - ii. Received counseling from the prescriber regarding:
 - 1) the risk of hepatotoxicity, the signs and symptoms of hepatotoxicity and, as appropriate, the risk of embryo-fetal toxicity and the need to use reliable contraception
 - 2) the need to complete liver function testing and, as appropriate, pregnancy testing as outlined in the *Bosentan REMS Program Guide for Patients*
 - 3) the Bosentan REMS Program contacting him/her prior to each dispense of bosentan to confirm that liver function tests and, as appropriate, pregnancy test were completed and provide counseling
- b. Bosentan Sponsors must:
 - i. Provide all the following mechanisms for the certified prescribers to be able to submit the completed *Bosentan REMS Program Patient Enrollment Form* to the Bosentan REMS Program: online, mail, fax
 - ii. Ensure that the certified outpatient pharmacy is able to verify bosentan is dispensed to patients only if there is evidence or other documentation that they have met the following requirements:
 - 1) Prescriber is certified
 - 2) Patient is enrolled

- 3) Patient has completed the liver function tests and each female of reproductive potential has completed the pregnancy test
 - 4) Patient has been counseled on the risk of hepatotoxicity and each female of reproductive potential has been counseled on the risk of embryo-fetal toxicity and the need to use reliable contraception
- iii. Before each outpatient dispensing, ensure the Bosentan REMS Program Contact Center:
- 1) Confirms and documents each patient has completed the liver function tests and each female of reproductive potential has completed the pregnancy test. If unable to obtain confirmation from the patient that the testing was completed, or if the patient cannot be reached, obtain confirmation from the patient's prescriber
 - 2) If the patient's prescriber cannot confirm that the required testing was completed, the Bosentan REMS Program Contact Center will:
 - a) Remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for females of reproductive potential)
 - b) Ask the prescriber whether or not he/she authorizes the refill of bosentan. The patient is eligible to receive a 30-day supply of bosentan only if the prescriber authorizes the refill
 - c) Document the prescriber's decision to authorize the refill in the Bosentan REMS Program system and notify to the dispensing pharmacy of the authorization
 - 3) Counsels the patient on the risk of hepatotoxicity, the signs and symptoms of hepatotoxicity and, as appropriate, the risk of embryo-fetal toxicity and need to use reliable contraception
- iv. Ensure the certified outpatient pharmacies receive authorization from the Bosentan REMS Program before each dispensing of bosentan
- v. Provide all the following mechanisms for outpatient pharmacies to obtain a pre-dispense authorization via accessing the Bosentan REMS Program Website, calling the Bosentan REMS Program Contact Center, or by using the REMS Pharmacy Network
- vi. Provide all the following mechanisms for certified inpatient pharmacies to verify prescriber certification and patient enrollment: accessing the Bosentan REMS Program Website or calling the Bosentan REMS Program Contact Center

- vii. Ensure that the certified pharmacies complete the verifications required under [Section A.II.2](#) for patients prior to dispensing
- viii. Ensure that the Bosentan REMS Program Contact Center updates the Bosentan REMS Program system with a patient's change in reproductive status within one business day of receipt of a completed *[Bosentan REMS Program Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form](#)*

B. Implementation System

1. Bosentan Sponsors must ensure that Bosentan is only distributed to certified pharmacies by:
 - a. Ensuring that wholesalers/distributors who distribute bosentan comply with the program requirements for wholesalers/distributors. The wholesalers/distributor must:
 - i. Put processes and procedures in place to verify, prior to distributing bosentan, that the pharmacy is certified
 - ii. Train all relevant staff on the Bosentan REMS Program requirements
 - iii. Comply with audits 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. In addition, wholesalers/distributors must maintain appropriate documentation and make it available for audits
 - iv. Provide complete, unblended and unblocked distribution data, including information on shipment to pharmacies to the Bosentan Sponsors to verify compliance with the Bosentan REMS Program
 - b. Ensuring that wholesalers/distributors maintain distribution records of all shipments of bosentan and provide the data to the Bosentan Sponsors
2. Bosentan Sponsors must monitor distribution data to ensure all the processes and procedures are in place and functioning to support the requirements of the Bosentan REMS Program
3. Bosentan Sponsors must audit the wholesalers/distributors within 180 calendar days after the wholesaler/distributor is authorized to ensure that all processes and procedures are in place and functioning to support the requirements of the Bosentan REMS Program. Corrective action must be instituted by Bosentan Sponsors if noncompliance is identified
4. Bosentan Sponsors must maintain a validated, secure database of pharmacies who are certified to dispense bosentan in the Bosentan REMS Program

5. Bosentan Sponsors must maintain records of bosentan distribution and dispensing, certified prescribers, certified pharmacies, wholesalers/distributors, and enrolled patients to meet REMS requirements
6. Bosentan Sponsors must maintain a Bosentan REMS Program Contact Center (1-866-359-2612) and *Bosentan REMS Program Website*. The *Bosentan REMS Program Website* must include the capability to complete prescriber and pharmacy certification online, the capability to enroll and manage patients online, the capability to verify prescriber certification and patient enrollment online, the option to print the Prescribing Information, and Bosentan REMS Program materials. Bosentan product websites must include a prominent REMS-specific link to the *Bosentan REMS Program Website*. The *Bosentan REMS Program Website* must not link back to the product websites
7. Bosentan Sponsors must ensure that within 30 calendar days of REMS approval the *Bosentan REMS Program Website* is fully operational and the REMS materials listed in or appended to the Bosentan REMS Program document are available through the *Bosentan REMS Program Website* or by calling the Bosentan REMS Program Contact Center
8. Bosentan Sponsors must monitor on an ongoing basis the certified pharmacies to ensure the requirements of the Bosentan REMS Program are being met. Bosentan Sponsors must institute corrective action if noncompliance is identified and decertify pharmacies that do not maintain compliance with the REMS requirements
9. Bosentan Sponsors must maintain an ongoing annual audit plan that involves wholesalers/distributors and pharmacies
10. Bosentan Sponsors must audit 10 pharmacies or one percent (1%), whichever is greater, of the certified pharmacies within 180 calendar days after the pharmacy places its first order of bosentan to ensure that all processes and procedures are in place and functioning to support the requirements of the Bosentan REMS Program. The certified pharmacies must also be included in Bosentan Sponsors ongoing annual audit plan. Bosentan Sponsors must institute corrective action if noncompliance is identified
11. Bosentan Sponsors must take reasonable steps to improve implementation of and compliance with the requirements in the Bosentan REMS Program based on monitoring and evaluation of the Bosentan REMS Program

C. Timetable for Submission of Assessments

Bosentan NDA Sponsors must submit REMS assessments to the FDA annually from the date of the initial approval of the Bosentan REMS Program (MM/DD/YYYY).

To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each annual assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. The Bosentan NDA Sponsors must submit each assessment so that it will be received by FDA on or before the due date.