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NDA 21290

Tracleer[ⓧ] (bosentan)

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Risk Evaluation and Mitigation Strategy (REMS)

I. GOAL(S)

The goals of the Tracleer REMS are:

1. To inform prescribers, patients, and pharmacists about the risks of Tracleer
2. To minimize the risk of hepatotoxicity in patients who are exposed to Tracleer
3. To minimize the risk of fetal exposures in female patients who are exposed to Tracleer
4. To educate prescribers, patients, and pharmacies on the safe-use conditions for Tracleer

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Tracleer prescription in accordance with 21 CFR 208.24.

The *Tracleer Medication Guide* is part of the REMS and is appended.

B. Elements to Assure Safe Use

- 1. Healthcare providers (HCPs) who prescribe Tracleer will be specially certified.**
 - a. Actelion will ensure that HCPs who prescribe Tracleer are specially certified. Actelion will ensure that to become certified, each prescriber agrees on the *Tracleer REMS Prescriber Enrollment and Agreement Form* to:
 - i. Read the full prescribing information (PI), the *Tracleer Medication Guide* and the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*

- ii. Enroll patients in the Tracleer REMS program by completing the *Tracleer Patient Enrollment and Consent Form*
- iii. Advise all patients that Tracleer is only available through a restricted distribution program called the Tracleer REMS program
- iv. Review the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients* with the patient prior to initiating treatment.
- v. Order and review pretreatment liver function tests and determine whether each female is of reproductive potential as defined in the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*
- vi. Order and review monthly liver tests
- vii. Notify Actelion of any adverse events, including hepatotoxicity, and report any pregnancy with all available information during treatment with Tracleer
- viii. Counsel patients who fail to comply with program requirements
- ix. For Females of Reproductive Potential (FRP):
 - 1) Counsel patients about the risk of teratogenicity and need to use reliable contraception as defined in the *Tracleer REMS Guide for Patients* during Tracleer treatment and for one month following treatment discontinuation, and her medical options in the event of unprotected sexual intercourse or known or suspected contraception failure
 - 2) Order and review pregnancy tests prior to initiation of Tracleer treatment, monthly during treatment, and for one month following treatment discontinuation
 - 3) Counsel the patient to immediately contact her healthcare provider if she misses a menstrual period or suspects that she is pregnant.
 - 4) Report a change or misclassification in reproductive status of any female patient by completing the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change
- x. For females of non-reproductive Potential (FNRP) will:
 - 1) Pre-pubertal patients:
 - a) Counsel the patient and/or a parent/guardian about the risk of teratogenicity.
 - b) Counsel the patient and/or a parent/guardian to immediately contact her healthcare provider if the patient begins to menstruate
 - c) Evaluate patients age 8 and older at least annually for any change in reproductive status and complete the *Tracleer REMS Change in*

Reproductive Potential Status and Pre-pubertal Annual Verification Form verifying their reproductive potential status

- d) Report a change or misclassification in reproductive status by completing the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change

2) Post-menopausal patients:

- a) Report a change or misclassification in reproductive status by completing the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change

3) Females with other medical reason for permanent, irreversible infertility (as defined by the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*):

- a) Report any change or misclassification in reproductive status by completing the *Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within ten (10) business days of becoming aware of the change

b. Actelion will:

- i. Ensure that prescribers' information and date of certification is linked to their enrolled patients' information in the validated secure Tracleer REMS Program database
- ii. Ensure that the patient information from a new prescriber is linked in the Tracleer REMS Program database with certification information from the prior prescriber
- iii. Maintain a valid secure database of certified prescribers in the REMS program. Actelion will ensure that the prescribers' certification requirements are met and will monitor prescription data and may de-enroll noncompliant prescribers until the requirements are met
- iv. Maintain a qualified secure database that links adverse events of interest extracted from the Drug Safety Database (Argus Safety™) with relevant information, such as enrolled patients, certified prescribers and certified pharmacies
- v. The revised Tracleer REMS Program Website will be available within 60 days after REMS modification approval. All materials listed in or appended to the Tracleer REMS Program will be available through the Tracleer REMS Program Website (www.TracleerREMS.com) or by calling Actelion Pathways® at 1-866-228-3546.

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

- i. Tracleer REMS Prescriber Enrollment and Agreement Form*
- ii. Tracleer Patient Enrollment and Consent Form*
- iii. Prescriber and Pharmacy Guide for the Tracleer REMS Program*
- iv. Tracleer REMS Guide for Patients*
- v. Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- vi. Dear Healthcare Provider Letter*
- vii. Tracleer REMS website*

2. Pharmacies that dispense Tracleer will be specially certified.

Outpatient Dispensing

- a. Actelion will ensure that pharmacies that dispense Tracleer are specially certified. Actelion will ensure that to be certified, pharmacies have a representative who is trained on the Tracleer REMS program and who attests that they will:
 - i. Train all dispensing staff on the Tracleer REMS Program procedures and REMS materials prior to dispensing Tracleer
 - ii. Agree that the certified pharmacy may be audited by the Food and Drug Administration (FDA), Actelion, or a third party designated by Actelion
 - iii. Put processes and procedures in place to ensure the following REMS requirements are met
 - a) Receive and accept prescriber and patient enrollment forms only from Actelion Pathways
 - b) Only dispense to patients who have a prescription written by a prescriber enrolled in the Tracleer REMS Program
 - c) Dispense Tracleer only to patients enrolled in the Tracleer REMS program
 - d) Provide a *Medication Guide* each time Tracleer is dispensed
 - e) Not transfer Tracleer to any pharmacy, practitioner, or healthcare setting not certified by Actelion Pathways
 - f) Verify reproductive status of females with information provided by Actelion Pathways prior to each dispensing of Tracleer
 - g) Counsel patients on the risk of hepatotoxicity and the need for monthly liver testing
 - h) Speak with each patient, or their prescriber, every month to obtain confirmation that liver function testing and pregnancy testing was completed
 - i) For FRP patients:
 - 1) Counsel patients on the risk of serious birth defects and the need to use reliable contraception, as defined in the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*, during Tracleer treatment and for one month after treatment discontinuation
 - 2) Inform patients of the need to complete a monthly pregnancy test and to inform their prescriber immediately if they suspect they are pregnant

- 3) Dispense up to a 30-day supply of Tracleer upon completing the following process:
 - a) Obtain confirmation from the patient that the appropriate testing was completed
 - b) 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
 - c) If the patient's prescriber cannot confirm that the required testing was completed, the certified pharmacy will:
 - i. Remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for FRP)
 - ii. Ask the prescriber whether or not he/she authorizes the refill of Tracleer. The patient is eligible to receive a 30-day supply of Tracleer only if the prescriber authorizes the refill of Tracleer
 - iii. Notify Actelion of any reports of adverse events, including hepatotoxicity, and any reports of pregnancy
 - iv. Agree to collect and report to Actelion specific data requirements needed to ensure compliance with the Tracleer REMS program including shipment records for every time Tracleer is dispensed. Actelion maintains the data in the Tracleer REMS Program database
- b. Actelion will ensure that Actelion Pathways notifies certified pharmacies of a patient's change in reproductive status within one business day of receipt of a completed *Tracleer REMS Change in Reproductive Potential Status and Prepubertal Annual Verification Form*.

Inpatient Dispensing

- a. Actelion will ensure that only inpatient pharmacies (including, but not limited to, inpatient pharmacies in hospitals, long-term care facilities, prisons, and state psychiatric units) that are certified in the Tracleer REMS Program may stock and dispense Tracleer for patients being treated in the inpatient setting. In order for an inpatient pharmacy to become certified in the Tracleer REMS Program, an authorized representative must complete and submit a *Tracleer REMS Inpatient Pharmacy Enrollment Form*, agreeing to:
 - i. To complete training in the Tracleer REMS Program
 - ii. Train all dispensing staff on the Tracleer REMS Program requirements and Tracleer REMS materials before they dispense Tracleer
 - iii. Audits by the FDA, Actelion, or a third party designated by Actelion

- iv. Put processes and procedures in place to ensure the REMS requirements are met
 - a) Tracleer will only be dispensed to inpatients who are under the supervision and care of a healthcare provider who has been certified in the Tracleer REMS Program
 - b) Tracleer will only be dispensed to inpatients who are already enrolled in the Tracleer REMS Program or who will be enrolled prior to discharge from the hospital.
 - c) No more than a fifteen day supply of Tracleer can be dispensed upon discharge of the patient
 - d) Not transfer Tracleer to any pharmacy, practitioner or healthcare setting not certified by Actelion Pathways
- v. To report adverse reactions to Actelion including hepatotoxicity, and to report any pregnancy during treatment with Tracleer
- vi. To develop a system to track its compliance with the conditions above and provide information about its compliance to Actelion and/or the Food and Drug Administration upon request
 - a) Certified inpatient pharmacies will only be able to acquire Tracleer through certified wholesale pharmacies
 - b) Actelion will manage the certification of inpatient pharmacies and provide the appropriate information to certified wholesale pharmacies
 - c) Actelion will manage certified wholesale pharmacies to track inventory of Tracleer
 - d) The following materials are part of the REMS and are appended:
 - *Tracleer REMS Inpatient Pharmacy Enrollment Form*

3. Tracleer will be dispensed to patients with evidence or other documentation of safe-use conditions:

- a. Actelion will ensure that to become enrolled each patient consents to participate in the program for as long as they are taking the medication by completing the *Tracleer Patient Enrollment and Consent Form*.

In order to become enrolled, all patients must agree:

- a) To read the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients*
- b) To have liver function testing prior to initiation of treatment and monthly thereafter until stopping Tracleer

- c) To be contacted prior to each dispensing of Tracleer to obtain confirmation that liver testing was completed
- d) To be counseled on the requirements of the Tracleer REMS program and the risk of hepatotoxicity

In addition, in order to become enrolled all FRPs must agree:

- a) To have a pregnancy test prior to initiation of treatment with Tracleer, monthly during Tracleer treatment, and for one month after stopping Tracleer
- b) To be counseled each month by the pharmacy on the need to use reliable contraception during Tracleer treatment and for one month after stopping Tracleer treatment
- c) To be contacted prior to each dispensing of Tracleer to obtain confirmation that pregnancy testing was completed
- d) To be counseled on the requirements of the Tracleer REMS program and the risk of serious birth defects
- e) To immediately notify her healthcare provider if she misses a menstrual period or suspects that she is pregnant
- f) To be contacted by Actelion if she becomes pregnant while on Tracleer or within one month after treatment discontinuation

C. Implementation System

The Implementation System includes the following:

1. Actelion will maintain a validated secure database of certified pharmacies and patients enrolled in the Tracleer REMS Program to monitor and evaluate implementation of the elements under Section B.2. and B.3. above.
2. Actelion will monitor the distribution of Tracleer to ensure that the drug is only shipped to certified pharmacies.
3. Actelion will monitor distribution and prescription data to ensure that only certified pharmacies are distributing and dispensing Tracleer. Actelion will include all certified outpatient pharmacies and Actelion Pathways in the company's annual audit plans to ensure they are implementing the Tracleer REMS program as directed.
4. Actelion will monitor and evaluate implementation of elements provided under Section B.2. and B.3. and if needed, take steps to improve implementation of these elements.
5. Actelion will monitor certified inpatient and outpatient pharmacies to ensure compliance with the Tracleer REMS Program and institute corrective actions if they are non-compliant.

6. Actelion will maintain Actelion Pathways to support patients, prescribers, certified pharmacies, and distributors in interfacing with the Tracleer REMS Program.
7. Actelion will ensure that all materials listed in or appended to the Tracleer REMS Program will be available through the Tracleer REMS Program Website (www.TracleerREMS.com) or by calling Actelion Pathways at 1-866-228-3546.

D. Timetable for Submission of Assessments

Actelion will submit REMS assessments for Tracleer REMS to FDA, annually on January 19th. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Actelion will submit each assessment so that it will be received by the FDA on or before the due date.