NDA 21-290

Tracleer (bosentan)
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Risk Evaluation Mitigation Strategy (REMS)

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I. GOAL(S)

The goals of the Tracleer risk evaluation and mitigation strategy are as follows:

1. To enable informed risk-benefit decisions for treating patients with 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 30-day supply of Tracleer and in accordance with 21 CFR 208.24.

B. Elements to Assure Safe Use

1. Tracleer will only be prescribed by healthcare professionals who are certified by Actelion under 505-1(f)(3)(A)
    a. Actelion will ensure that physicians and other appropriately licensed healthcare providers who prescribe Tracleer are specially certified. Actelion will ensure that each prescriber agrees, on the Prescriber Certification section of the Tracleer Enrollment and Renewal Form each time he or she prescribes Tracleer, that he or she has read and understood the Tracleer Prescriber Essentials training guide and documented that he or she:
        i. Has enrolled patients in the REMS program (the Tracleer Access Program [T.A.P]), and documented eachenrollment.
        ii. Has reviewed and discussed the Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with their patients prior to prescribing Tracleer
        iii. Has reviewed pretreatment liver function tests and confirmed that Female patients of Child Bearing Potential (FCBP) are not pregnant
        iv. Has ordered and will monitor monthly liver tests and for FCBP, pregnancy tests
        v. Has educated and counseled any FCBP to notify the prescriber if she suspects she might be pregnant

vi. Has educated and counseled any FCBP about the need to use reliable methods of contraception during treatment with Tracleer and for one month after treatment discontinuation
vii. Will notify Actelion of any adverse events, including hepatotoxicity, and to report any pregnancy during treatment with Tracleer
viii. Will counsel patients who fail to comply with program requirements
ix. For patients continuing therapy, will re-enroll patients into the REMS program after the first 12 months of treatment then annually thereafter

b. Actelion will

i. Ensure that prescribers' enrollment information and date of certification is linked to their enrolled patients' information in a validated (T.A.P.) database

ii. Ensure that the patient information from a new prescriber is linked in the T.A.P. database with information from the prior prescriber

iii. Any prescribers who have had fewer than six patients on bosentan will be retrained at 6 months following the initial patient enrollment and training. A copy of the Essentials kit and a reminder letter will be sent to these prescribers to remind them of the risks of Tracleer and the need for ongoing monitoring to assure safe use of Tracleer

iv. Maintain a database of certified prescribers in the REMS program. Actelion will monitor prescribers' certification requirements and prescription data and may de-enroll noncompliant prescribers until the requirements are met

v. Create a new reporting database that will link adverse events of interest extracted from the Drug Safety Database (Argus Safety™) with relevant information, such as enrolled patients, certified prescribers and pharmacies.

vi. Generate a report each month from the T.A.P. database to identify any prescription that exceeds a 30-day supply.

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

i. Tracleer Enrollment and Renewal Form

ii. Prescriber Essentials guide

iii. Prescriber letter

2. Tracleer will only be dispensed by pharmacies, practitioners, and health care settings (dispensers) that are specially certified by Actelion under 505-1(f)(3)(B).

a. Actelion will ensure that Tracleer dispensers are specially certified. Tracleer will only be dispensed by pharmacies that are specially certified. Actelion will ensure that, to be certified, they are under legal contract and that they will:

i. Receive and accept prescriber and patient enrollment forms only from PAH Pathways, the entity that administers TAP.

ii. Counsel patients

    1. on the risks of Tracleer, including the risks of liver injury and serious birth defects

    2. on the need to complete a monthly liver function test and pregnancy test (for FCBP as defined on the Tracleer Enrollment and Renewal Form)

iii. Counsel all FCBP on the need to use reliable contraception (as defined in the Tracleer Enrollment and Renewal Form) during Tracleer treatment and for one month after treatment discontinuation, and the need to inform their prescriber if they suspect they may be pregnant

iv. For product that will be dispensed and shipped to the patient, confirm the drug shipment address with the patient

v. Dispense Tracleer only as 30-day supplies (except as described below) and require monthly refills

vi. Dispense Tracleer only to patients enrolled in the REMS program

vii. Provide a Medication Guide to patients each time Tracleer is dispensed

viii. Speak with each patient, or their prescriber, every month to obtain confirmation that liver function testing and pregnancy testing was completed.

ix. Dispense a 30-day supply of Tracleer (for patients not traveling outside the United States for more than 30 days) only upon completing the following process:

    1. Obtain confirmation from the patient that the testing was completed.

    2. 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.

    3. If the patient's prescriber cannot confirm that the required testing was completed, the certified pharmacy will:

        a. Remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for FCBP)

        b. 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.

x. For patients traveling outside the United States for more than 30 days, the following process must be completed:

1. The certified pharmacy is notified by an enrolled patient and/or certified prescriber of the need to fulfill a greater than 30-day supply due to the patient's extended travel outside the US.

2. The certified pharmacy contacts the patient and the prescriber to verify the need. The certified pharmacy explains the process to the patient, and tells them that the form (FRM-549-COP-US) will be sent to the certified prescriber for completion and submission.

3. The certified pharmacy provides the prescriber with a letter explaining the process, and the request form (FRM-549-COP-US).

4. The certified prescriber completes the form and faxes it to the certified pharmacy.

5. The certified pharmacy reviews the form for completeness and contacts either the certified prescriber or the patient to obtain any additional information.

6. The medication is shipped to the patient, along with the Medication Guide and the required patient information sheet.

7. The certified pharmacy documents in their data management system that the patient met the criteria for the greater than 30-day supply due to foreign travel. This information is sent to Actelion as usual with the dispensed amount (in tablets), dose, and frequency captured.

8. The certified pharmacy contacts the prescriber for the monthly call in this situation to determine if safe-use conditions are being followed by the patient and prescriber. This is documented in the certified pharmacy data management system.

xi. Call patients, who discontinue Tracleer treatment, or their prescriber, to determine the reason for treatment discontinuation and record this information for inclusion in the T.A.P. validated database

xii. Notify Actelion of any reports of adverse events, including liver injury, and any reports of pregnancy.

xiii. 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 T.A.P. database.

b. Actelion will ensure that a designated representative of each certified pharmacy:

i. is trained on the REMS program.

ii. trains pharmacy staff on the REMS program procedures and REMS materials prior to dispensing Tracleer

iii. agrees that the certified pharmacy may be audited by the FDA, Actelion, or a third party designated by Actelion

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

i. FRM 549-COP-US, Request for > 30-Day Supply.

ii. Prescriber letter from certified pharmacy (accompanies FRM-549-COP-US)

iii. Patient Information Sheet (to be provided to the patient by the certified pharmacy)

3. Tracleer will only be dispensed to patients with evidence or other documentation of safe-use conditions under 505-1(f)(3)(D):

a. Actelion will ensure that patients treated with Tracleer are enrolled in the REMS program and assigned a unique identifying number before Tracleer is dispensed to him or her. 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 acknowledging that he or she:

i. has read the Tracleer Medication Guide and patient educational materials and

ii. agrees to be contacted, prior to each shipment of Tracleer, to obtain confirmation that liver function testing and, if applicable, pregnancy testing was completed and

iii. agrees to be counseled on the requirements of the REMS program and the risks of Tracleer.

iv. acknowledges, in the case of a FCBP, that she will be contacted to respond to a preganancy questionnaire if she becomes pregnant while on Tracleer.

b. Actelion will ensure that, to continue receiving Tracleer, each patient is re-enrolled every 12 months following their initial enrollment.

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

i. Patient Essentials Guide

C. Implementation System

The Implementation System includes the following:

1. Actelion will maintain a database capturing certified prescribers, pharmacies and patients. Actelion will create a new reporting database that will link adverse events

of interest extracted from the Drug Safety database (Argus Safety™) with relevant information, such as enrolled patients, certified prescribers and pharmacies.

2. Actelion will monitor distribution and prescription data to ensure that only certified pharmacies are distributing and dispensing Tracleer. The certified pharmacies are the only distributors of Tracleer. Therefore, the distribution data will be the same as the prescription data.

3. Actelion will audit all certified pharmacies against their formal procedures and contractual arrangements at least once every 12 months and more frequently if non-compliance issues are identified.

4. Actelion will ensure that the pharmacies follow an agreed upon, scripted process to follow when a patient is identified as non-compliant with the testing, or the compliance with the required testing is uncertain in the previous month. The scripted process includes steps whereby the pharmacy provides prompt feedback to the prescriber on the potential non-compliance circumstances and reminds the prescriber of the need for ongoing monitoring. The pharmacies record their actions, and notify T.A.P.

5. Actelion will collect information from the pharmacies about compliance with hepatic and pregnancy testing and monitor the data in the T.A.P. database.

D. Timetable for Submission of Assessments

Following approval of the REMS and associated supplements, as appropriate, the REMS assessments will be submitted to FDA annually. The assessment interval period will close no earlier than 60 days prior to the date the respective assessment is due. The assessment is to be received by the FDA on the due date.