NEW SUPPLEMENT FOR NDA 21-290
Tracleer (bosentan)
Actelion Clinical Research, Inc.
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Risk Evaluation Mitigation Strategy (REMS)
REMS MODIFICATION

November 15, 2012

Document No: D-12.636
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, hospitals, 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 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 for Patients and Prescribers form or the Prescriber Certification Form 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 each enrollment.

      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 the 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 of record

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. Maintain a reporting 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.

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

vii. Within 60 (sixty) days of the modified REMS approval, a Dear Prescriber Letter will be sent to all certified prescribers to explain (to physicians and other appropriately licensed healthcare providers who prescribe Tracleer) the new requirement for hospital certification for the inpatient use of Tracleer as well as inform them of the availability of the blister package for unit dosing in the hospital. The letter will be accompanied by the Full Prescribing Information, and will also be
available on the Tracleer REMS website for 1 year from the date of the mailing.

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

- Tracleer Enrollment for Patients and Prescribers forms
- Prescriber Essentials guide
- Prescriber Certification form
- Tracleer Renewal form
- Dear Prescriber Letter
- Tracleer REMS website

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

a. Outpatient Dispensing -

Tracleer will only be dispensed by outpatient pharmacies that are specially certified. Actelion will ensure that, to be certified, pharmacies are under legal contract and 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 hepatotoxicity and serious birth defects

2. on the need to complete a monthly liver function test and pregnancy test (for FCBP as defined in the Tracleer Product Information)

iii. Counsel all FCBP on the need to use reliable contraception (as defined in the Tracleer Product Information) 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 and Monthly Reminder Wallet card 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. database.

xii. Notify Actelion of any reports of adverse events, including hepatotoxicity, 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.

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

- is trained on the REMS program.
- trains pharmacy staff on the REMS program procedures and REMS materials prior to dispensing Tracleer.
- agrees that the certified pharmacy may be audited by the FDA, Actelion, or a third party designated by Actelion.

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

- FRM 549-COP-US, Request for > 30-Day Supply.
b. Inpatient Dispensing -

Actelion will ensure that Tracleer is only dispensed in the inpatient setting by certified hospitals.

i. To be certified, a hospital must have an authorized designee complete and agree to the requirements in the Tracleer Access Program Hospital Certification Form and provide completed form to Actelion. The authorized designee acknowledges that:

1. The hospital will establish systems, order sets, protocols, or other measures to limit the use of Tracleer as outlined below and to ensure appropriate liver function and pregnancy tests are performed.
2. 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 Access Program.
3. Tracleer will only be dispensed to inpatients who are already enrolled in the Tracleer Access Program or who will be enrolled prior to discharge from this hospital.
4. The hospital will dispense no more than a seven (7) day supply of Tracleer in a child-resistant container upon discharge of the patient.
5. A Tracleer Medication Guide will be provided to the patient prior to discharge from this hospital. (Available for download at www.TRACLEERREMS.com)
6. The hospital agrees to report adverse reactions to Actelion Pharmaceuticals US, Inc., including hepatotoxicity, and to report any pregnancy during treatment with Tracleer.
7. The hospital agrees to re-certify every three (3) years.
8. The hospital agrees 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.
ii. Actelion will ensure that within 60 (sixty) days of the modified REMS approval, a Dear Hospital Letter will be sent. The target audience for the letter will be pharmacy directors at hospitals who have a history of dispensing Tracleer or who have a known affiliation with healthcare providers who specialize in the treatment of pulmonary arterial hypertension as identified via a national patient organization. The letter will explain the new requirement for hospital certification for inpatient use of Tracleer and the availability of the blister package for unit dosing. The letter will also be available on the Tracleer REMS website for 1 year from the date of the mailing.

iii. Certified hospitals will only be able to acquire Tracleer through certified wholesale pharmacies.

iv. Actelion will manage the certification of hospitals and provide the appropriate information to certified wholesale pharmacies.

v. Actelion will manage certified wholesale pharmacies to track inventory of Tracleer.

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

- Tracleer Access Program Hospital Certification Form
- Dear Hospital Letter

3. Tracleer will only be dispensed for outpatients use 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 in the outpatient setting. 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 pregnancy 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 by their certified prescriber.

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

- Patient Essentials Guide
- Monthly Reminder Wallet Card

C. Implementation System

The Implementation System includes the following:

1. Actelion will maintain a database capturing certified prescribers, certified pharmacies, certified wholesale pharmacies, certified hospitals and enrolled patients.

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.

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 certified 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 certified pharmacies about compliance with hepatic and pregnancy testing and monitor the data in the T.A.P. database.

6. Actelion will evaluate certified hospitals who dispense Tracleer in the inpatient setting at least once every twelve (12) months and more frequently if non-compliance issues are identified.

D. Timetable for Submission of Assessments

Actelion will submit REMS assessments 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.