Tracleer BOSENTAN TABLETS

The Tracleer® (bosentan) REMS (Risk Evaluation and Mitigation Strategy) Program

A Risk Evaluation and Mitigation Strategy (REMS) is a program required by the Food and Drug Administration (FDA) to manage serious risks associated with a drug product.

Because of the risks of hepatotoxicity and teratogenicity, Tracleer is available only through a restricted program called the Tracleer REMS Program. Under the Tracleer REMS, prescribers, patients, pharmacies, and hospitals must enroll in the program. In order to receive Tracleer, hospitals, prescribers, and patients must agree to comply with the requirements of the program. In addition, Tracleer is dispensed only through specialty pharmacies.

The goals of the Tracleer REMS Program are:

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

Indication

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).

Considerations for use: Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO class II patients, which may preclude future use as their disease progresses.

Tracleer REMS Program Overview

- All healthcare providers must enroll in the Tracleer REMS Program and comply with the REMS Program requirements in order to prescribe Tracleer
- All patients must enroll in the Tracleer REMS Program and comply with the REMS Program requirements in order to receive Tracleer
  - All patients must agree to be counseled on the Tracleer REMS Program and the risks of treatment with Tracleer
  - All patients must agree to be contacted about completing required monthly testing
- Prescribers must counsel all patients on the risks of Tracleer, including the risk of hepatotoxicity
- Prescribers must order and review liver function tests prior to initiation of treatment and monthly thereafter for all patients
- Prescribers must closely monitor transaminase levels and adjust monitoring and treatment with Tracleer if increases are reported
- Prescribers must discontinue Tracleer if liver aminotransferase elevations are accompanied by clinical symptoms of hepatoxicity or increases in bilirubin ≥2 ULN
- Prescribers must determine the reproductive status of female patients
- Prescribers must counsel Females of Reproductive Potential and Pre-pubertal Females, once they become Females of Reproductive Potential about the risks of Tracleer, including the risk of teratogenicity
- Prescribers must order and review pregnancy testing for Females of Reproductive Potential prior to initiation of treatment, monthly during treatment, and for one month after stopping treatment
- Prescribers must report any change or misclassification in a female's reproductive potential status to the Tracleer REMS Program
- Definitions of Reproductive Potential Status
  - Females of Reproductive Potential
    - Females of reproductive potential include girls who have entered puberty and all females who have a uterus and have not passed through menopause (as defined below)
    - For the purposes of this REMS, puberty includes those girls who are at least Tanner Stage 3 and have not yet had a menses (premenarchal)
  - Females of Non-Reproductive Potential
    - Pre-pubertal Females: Females who are at Tanner Stages 1 and 2 are not considered to be of reproductive potential
    - Post-menopausal Females: Females who have passed through menopause. Menopause is defined as 12 months of spontaneous amenorrhea (not amenorrhea induced by a medical condition or medical therapy) or post-surgical form bilateral oophorectomy
    - Females with other medical reasons for permanent, irreversible infertility
- For Females of Reproductive Potential:
  - Pregnancy must be ruled out prior to drug initiation, monthly during treatment, and for one month after stopping treatment
  - She must agree to be contacted by Actelion if she becomes pregnant either while on Tracleer or within one month of treatment discontinuation
- Only pharmacies certified in the Tracleer REMS Program can dispense Tracleer to outpatients
- Only inpatient pharmacies that are certified in the Tracleer REMS Program will stock Tracleer for inpatient use

Changes to the Tracleer REMS Program (November 2015)

- New definition of Female of Non-Reproductive Potential (Please see the *Prescriber and Pharmacy Guide for the Tracleer REMS Program* for the definitions)
- New form and process: *Tracleer REMS Change in Reproductive Potential Status and Prepubertal Annual Verification Form*
- New form: *Tracleer Patient Enrollment and Consent Form*
- New form: *Tracleer REMS Prescriber Enrollment and Agreement Form*
- No annual re-enrollment for all patients
- No annual re-certification for all prescribers
- No 3-year re-certification for Healthcare facilities

Materials for Prescribers

- *Prescriber and Pharmacy Guide for the Tracleer REMS Program*
- *Tracleer REMS Prescriber Enrollment and Agreement Form*
- *Tracleer Patient Enrollment and Consent Form*
- *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
- *Healthcare Provider Letter*

Materials for Patients

- *Tracleer REMS Guide for Patients*
- *Tracleer Medication Guide*

Materials for Pharmacies

- *Tracleer REMS Inpatient Pharmacy Enrollment Form*
- *Prescriber and Pharmacy Guide for the Tracleer REMS Program*
- *Healthcare Provider Letter*

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ACTELION

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Tracleer BOSENTAN TABLETS

The Tracleer® (bosentan) REMS (Risk Evaluation and Mitigation Strategy) Program

Tracleer REMS Program Overview

Changes to the Tracleer REMS Program

Certified Pharmacies

For Prescribers

Prescriber's Role in the Tracleer REMS Program

1. **Read the *Tracleer Prescribing Information* and the *Prescriber and Pharmacy Guide for the REMS Program* to understand the risks of Tracleer and to learn about the Tracleer REMS Program**
   - Prescribers must understand the risks of Tracleer and become familiar with the Tracleer REMS Program
2. **Complete a *Tracleer REMS Prescriber Enrollment and Agreement***
   - By signing the form, you attest to understanding the risks of Tracleer and agree to comply with the Tracleer REMS Program
   - You can download the *Tracleer REMS Prescriber Enrollment and Agreement Form* here and fax it to *Actelion Pathways*® at 1-866-279-0669. *Actelion Pathways* administers the Tracleer REMS Program
3. **Determine the reproductive potential for female patients**
   - Prescribers should identify female patients (captured on the *Tracleer REMS Patient Enrollment and Consent Form*) as one of the following categories:
     - Female of Reproductive Potential (FRP)

       or
     - Female of Non-Reproductive Potential (FNRP) (choose one of the options below)
       - Pre-pubertal Female of Non-Reproductive Potential
       - Post-menopausal Female of Non-Reproductive Potential
       - Female with other medical reasons for permanent, irreversible infertility

   Definitions are provided in the "Tracleer REMS Program Overview" section of the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*.
4. **Educate and counsel all patients about the risks of Tracleer**
   - For all patients, prescribers must:
     - Advise the patient that Tracleer is only available through a restricted distribution program called the Tracleer REMS Program
     - Educate and counsel patients about the risks of Tracleer, including the risk of hepatotoxicity
     - Provide the *Tracleer Medication Guide* to each patient and instruct him or her to read it
     - Advise the patient of the requirement for initial and monthly liver function tests to enable monitoring of their liver and so they can begin and continue to receive Tracleer
     - Counsel the patient to contact their healthcare provider immediately if they have signs or symptoms of liver injury such as nausea, vomiting, fever, unusual tiredness, stomach area (abdominal) pain, or yellowing of the skin or the whites of the eyes (jaundice)
     - Prescribers must counsel any patient who fails to comply with the program requirements
     - Counsel patients that they must agree to be contacted prior to each shipment to confirm that a liver function test and, if applicable, a pregnancy test, has been completed
   - For Females of Reproductive Potential, prescribers must:
     - Review with her the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients*
     - Educate her about the risk of teratogenicity, the need to use reliable contraception during Tracleer treatment and for one month following treatment discontinuation; as well as her need to consider medical options in the event of unprotected sexual intercourse or known or suspected contraception failure
     - Advise the patient of the requirement for initial and monthly pregnancy tests to confirm she is not pregnant, so she can begin and continue to receive Tracleer
     - Counsel her to immediately contact her healthcare provider if she misses a menstrual period or suspects she is pregnant
   - For Pre-pubertal Females of Non-Reproductive Potential, prescribers must:
     - Review with her and/or her parent/guardian the *Tracleer Medication Guide*
     - Educate her and her parent/guardian about the risk of serious birth defects
     - Counsel her and her parent/guardian to immediately contact her healthcare provider if she gets her menstrual period
5. **Enroll all patients into the Tracleer REMS Program by ensuring patients complete the *Tracleer Patient Enrollment and Consent Form***
   - Confirm the patient has agreed to comply with program requirements and has signed the form where indicated
   - Fax the completed form, along with all patient insurance information, including prescription drug benefits and medical benefits, to *Actelion Pathways*® at 1-866-279-0669. *Actelion Pathways* administers the Tracleer REMS Program
   - Keep the original form with the patient's records
6. **Check patient's liver function and pregnancy status (if patient is a Female of Reproductive Potential)**
   - Order and review liver function tests for all patients:
     - Prior to initiating treatment
     - Monthly during treatment
   - Order and review pregnancy tests for female patients of reproductive potential:
     - Prior to initiating treatment
     - Monthly during treatment
     - One month after stopping treatment
7. **Monitor all patients throughout treatment**
   - For all patients, prescribers must
     - Order and review liver function tests monthly during treatment with Tracleer
     - For changes in aminotransferase levels, adjust the monitoring and treatment with Tracleer
     - Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥ 2 x ULN
   - For Females of Reproductive Potential, prescribers must:
     - Order and review pregnancy tests monthly during treatment with Tracleer and for one month after stopping treatment
     - Notify the patient and Actelion if her pregnancy test is positive
     - Monitor patients' reproductive status during treatment with Tracleer and report any changes or misclassifications to the Tracleer REMS Program by completing and submitting the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
   - For Females of Non-Reproductive Potential, prescribers must:
     - Monitor patients' reproductive status during treatment with Tracleer and report any changes or misclassifications to the Tracleer REMS Program by completing and submitting the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
     - For each Pre-pubertal Female who is at least 8 years of age or older, annually verify and report the reproductive status by completing and submitting the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

Reporting to Actelion
To report any pregnancies and suspected adverse reactions, including liver injury, contact Actelion at 1-866-228-3546.
Reporting to FDA MedWatch
Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

Materials for Prescribers

- *Prescriber and Pharmacy Guide for the Tracleer REMS Program*
- *Tracleer REMS Prescriber Enrollment and Agreement Form*
- *Tracleer Patient Enrollment and Consent Form*
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- *Healthcare Provider Letter*

Materials for Patients

- *Tracleer REMS Guide for Patients*
- *Tracleer Medication Guide*

Materials for Pharmacies

- *Tracleer REMS Inpatient Pharmacy Enrollment Form*
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Tracleer BOSENTAN TABLETS

FOR PATIENTS | FOR PRESCRIBERS | FOR PHARMACIES

The Tracleer® (bosentan) REMS (Risk Evaluation and Mitigation Strategy) Program

Information for Patients

What is the Tracleer REMS (Risk Evaluation and Mitigation Strategy) Program?

The Tracleer REMS is a program to tell patients and healthcare providers about the risks of liver damage and serious birth defects when taking Tracleer. This program is required by the Food and Drug Administration (FDA). All patients must enroll in the Tracleer REMS Program to receive Tracleer. REMS stands for Risk Evaluation and Mitigation Strategy.

How do I enroll in the Tracleer REMS Program?

There are several steps you must take:

- Read the *Tracleer REMS Guide for Patients* and the *Tracleer Medication Guide* (which comes with your medicine)
- Ask your healthcare provider any questions you have about taking Tracleer and the Tracleer REMS Program
- Make sure you understand:
  - The benefits and risks of Tracleer
  - How to enroll and take part in the Tracleer REMS Program
- Complete and sign the *Tracleer Patient Enrollment and Consent Form* with your healthcare provider. Your healthcare provider will fill out most of the enrollment form for you and will send the form to *Actelion Pathways*®. *Actelion Pathways* runs the Tracleer REMS Program

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Pharmacy Certification

Due to the risk of hepatotoxicity and teratogenicity, Tracleer is only available through a network of certified pharmacies.

Outpatient Pharmacy Certification

Tracleer will be dispensed to outpatients by a limited number of certified pharmacies. Prior to dispensing Tracleer, the pharmacy will confirm that the prescriber who wrote the prescription and the patient are enrolled in the Tracleer REMS Program. If either the patient or prescriber is not enrolled, Tracleer will not be dispensed.

All patients will only be able to get a 30-day supply of Tracleer at one time. The *Tracleer Medication Guide* will be provided to all patients each time Tracleer is dispensed.

All patients will be contacted each month by the pharmacy to arrange dispensing of Tracleer.

For all patients, the pharmacy will:

- Ask if he/she has had a liver function test within the last month (30 days)

For Females of Reproductive Potential, the pharmacy will:

- Ask the patient if she has had a pregnancy test within the last month
- Counsel her on the need to use reliable contraception during Tracleer treatment and for one month after stopping treatment
- Counsel her to inform her prescriber immediately if she misses a menstrual period or suspects that she may be pregnant or if her reproductive status changes

For Pre-pubertal Females, the pharmacy will:

- Counsel her to inform her prescriber immediately if her reproductive status changes

Inpatient Pharmacy Certification

Only inpatient pharmacies (including, but not limited to, 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.

By certifying in to the Tracleer REMS Program, the inpatient pharmacy agrees to:

- Complete training in the Tracleer REMS Program by reading the *Prescribing Information*, *Medication Guide* and the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*
- Train all dispensing staff on the Tracleer REMS Program requirements and Tracleer REMS materials before they dispense Tracleer
- Put processes and procedures in place to ensure the REMS requirements are met
- Dispense only to those patients under the supervision and care of a healthcare provider who is enrolled in the Tracleer REMS Program
- Dispense to a patient only after he/she has been enrolled in the Tracleer REMS Program or if he/she will be enrolled prior to discharge from the healthcare facility. A patient who has not been enrolled by the certified prescriber will not have access to Tracleer in the outpatient setting until registration has been completed
- Dispense no more than a fifteen (15) day temporary supply of Tracleer upon discharge of any patient
- Notify Actelion or FDA of any adverse events, including hepatotoxicity, and report any pregnancy during Tracleer treatment
- Not transfer Tracleer to any pharmacy, practitioner or any healthcare setting not certified by *Actelion Pathways*
- Develop a process to track compliance with the conditions above and provide information about its compliance to Actelion

To be certified in the Tracleer REMS Program, an authorized representative of the inpatient pharmacy must:

- Agree to follow the REMS requirements by completing and submitting a *Tracleer REMS Inpatient Pharmacy Enrollment Form* to the Tracleer REMS Program
- Fax the completed form to *Actelion Pathways* at 1-866-279-0669
- Agree that the pharmacy may be subject to an audit by the FDA, Actelion, or a designated third party

If an inpatient pharmacy needs Tracleer and is not enrolled in the Tracleer REMS Program, the inpatient pharmacy can contact *Actelion Pathways* at 1-866-228-3546 for assistance in obtaining a 15 day supply of Tracleer while initiating enrollment.

Certified Pharmacies

For information on any changes to the list of Tracleer certified pharmacies, please call *Actelion Pathways*® at 1-866-228-3546.

Accredo Specialty Pharmacy
Aetna Specialty Pharmacy
Axium Healthcare Pharmacy
CVS Specialty Pharmacy
Cigna Pharmacy
Humana RightSource Specialty Pharmacy
Kaiser Specialty Pharmacy
OptumRx Specialty Pharmacy
Walgreens Specialty Pharmacy

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Contact Us

If you would like additional information regarding the Tracleer REMS Program, please contact *Actelion Pathways*® at 1-866-228-3546, Mon-Fri, 9 AM-8 PM ET.

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