Prescriber and Pharmacy Guide for the Tracleer® REMS Program

*Please see accompanying full Prescribing Information, including **BOXED WARNING** for hepatotoxicity and teratogenicity.*

ACTELION Pathways®

Tracleer® BOSENTAN TABLETS

Introduction to Tracleer® (bosentan)

Indication

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness in adults included predominantly patients with WHO 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%).
- In pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

Risk of hepatotoxicity

Tracleer may cause liver damage. Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.

Changes in aminotransferases may occur early or late in treatment. There have been rare postmarketing reports of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring; the contribution of Tracleer could not be excluded.

Elevations in aminotransferases require close attention. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. See the Tracleer aminotransferase (ALT/AST) management Table on page 7 for treatment and monitoring recommendations for liver enzyme elevations. Use of Tracleer should generally be avoided in patients with elevated aminotransferases (>3 × ULN) **at baseline** because monitoring for hepatotoxicity may be more difficult.

Risks of teratogenicity

Tracleer is contraindicated in females who are or may become pregnant and may cause fetal harm when administered to a pregnant woman. Animal studies have shown that Tracleer is likely to cause major birth defects when administered during pregnancy. If Tracleer is used during pregnancy, apprise the patient of the potential hazard to a fetus. To prevent pregnancy, females of reproductive potential must use reliable contraception during treatment and for one month after stopping Tracleer. Patients must not become pregnant while taking Tracleer.

Tracleer REMS (Risk Evaluation and Mitigation Strategy) Program

Due to the risk of hepatotoxicity and teratogenicity, Tracleer is only available through a restricted distribution program required by the FDA called the Tracleer REMS (**R**isk **E**valuation and **M**itigation **S**trategy) Program.

The goals of the Tracleer REMS Program 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

Please see accompanying full Prescribing Information, including ***BOXED WARNING*** *for hepatotoxicity and teratogenicity.*

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 hepatotoxicity 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 from 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

Summary of Tracleer REMS Program requirements

All prescribers must be enrolled in the Tracleer REMS Program in order to prescribe Tracleer. To become enrolled, a healthcare provider must complete a *Tracleer REMS Prescriber Enrollment and Agreement Form*, agreeing to follow the Tracleer REMS Program requirements. This form must be submitted to the Tracleer REMS Program.

All patients must be enrolled in the Tracleer REMS Program in order to receive Tracleer. To become enrolled, a patient must complete a *Tracleer REMS Patient Enrollment and Consent Form* with her or his prescriber, agreeing to follow the Tracleer REMS Program requirements. This form must be submitted to the Tracleer REMS Program.

Prescribers must determine and document on the *Tracleer REMS Patient Enrollment and Consent Form* whether the patient is a male, a Female of Reproductive Potential, or a Female of Non-Reproductive Potential (Pre-pubertal Female, Post-menopausal Female, or a female with other medical reasons for permanent, irreversible infertility). **This category must be documented on the *Tracleer REMS Patient Enrollment and Consent Form.*** (See "Definitions of Reproductive Potential Status").

Based on whether the patient is a male, Female of Reproductive Potential, or a Female of Non-Reproductive Potential (Pre-pubertal Female, Post-menopausal Female, or a female with other medical reasons for permanent, irreversible infertility), the prescriber must complete certain actions before initiating treatment, during treatment, and after the patient stops taking Tracleer.

Please see accompanying full Prescribing Information, including ***BOXED WARNING*** *for hepatotoxicity and teratogenicity.*

Summary of Tracleer® REMS Program requirements (continued)

Requirement	All Patients	Females of Reproductive Potential	Females of Non-Reproductive Potential	
			Pre-pubertal	Post-menopausal or other medical reasons for permanent, irreversible infertility
Prescriber enrolls patients into Tracleer REMS Program	●			
Prescriber counsels with *Tracleer REMS Guide for Patients*	●			
Prescriber counsels with *Tracleer Medication Guide*, including the risk of hepatotoxicity and teratogenicity	●*			
Prescriber must order and review liver function tests prior to initiation of treatment and monthly during treatment	●			
Prescriber must order and review pregnancy tests prior to initiation of treatment, monthly during treatment, and for 1 month after stopping treatment		●		
Prescriber must verify reproductive status annually in Pre-pubertal patients 8 years of age or older by completing the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*			●	
Prescriber must complete the *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* upon becoming aware of any change or misclassification in reproductive potential status within 10 business days of awareness		●	●	●

*Counsel Pre-pubertal Female patient and/or parent/guardian.

The table below provides recommendations on managing Tracleer patients with elevated liver function test results. Elevated monthly liver function test results do not preclude treatment with Tracleer.

Tracleer aminotransferase (ALT/AST) management

ALT/AST level	Treatment and monitoring recommendations
≤3 × ULN*	**Continue** to monitor; no change in monitoring schedule or dosage
>3 to ≤5 × ULN	**Confirm** by another aminotransferase test; if confirmed, • in adults and pediatric patients >12 years and >40 kg, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values, treatment may continue or be reintroduced at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. • in all other pediatric patients, interrupt treatment with no prior dose reduction. If the aminotransferase levels return to pretreatment values, reintroduce at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
>5 to ≤8 × ULN	**Confirm** by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, • in adults and pediatric patients >12 years and >40 kg, consider reintroduction of treatment at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. • in all other pediatric patients, consider reintroduction at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
>8 × ULN	**Stop** treatment permanently. There is no experience with reintroduction of Tracleer in these circumstances.

*ULN-Upper limit of normal.
†If Tracleer is reintroduced it should be at the starting dose; aminotransferase levels should be checked within 3 days.

Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

*Please see accompanying full Prescribing Information, including **BOXED WARNING** for hepatotoxicity and teratogenicity.*

Prescriber's Role in the Tracleer® REMS Program

Healthcare providers must complete the following steps in the Tracleer REMS Program:

1. **Read** the Tracleer Prescribing Information and this guide to understand the risks of Tracleer and to learn about the Tracleer REMS Program
2. **Complete** a *Tracleer REMS Prescriber Enrollment and Agreement Form*
3. **Determine** the reproductive potential of female patients
4. **Educate and counsel** all patients about the risks of Tracleer
5. **Enroll** all patients into the Tracleer REMS Program by completing a *Tracleer REMS Patient Enrollment and Consent Form*
6. **Check** patient's liver function and pregnancy status (if patient is a Female of Reproductive Potential)
7. **Monitor all patients throughout treatment**

   Monitor liver function for ALL patients throughout treatment

   Monitor pregnancy and reproductive potential status for female patients throughout treatment

The next section provides specific information on each step:

1. **Read the Tracleer Prescribing Information and this guide 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 Form***
   - 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* from the Tracleer REMS website 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 section "Tracleer REMS Program overview."
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 tests to enable monitoring of their liver function 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 your 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

Please see accompanying full Prescribing Information, including ***BOXED WARNING*** *for hepatotoxicity and teratogenicity.*

- 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; and 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. <u>Enroll</u> all patients into the Tracleer REMS Program by ensuring patients complete the *Tracleer REMS 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. <u>Check</u> 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. <u>Monitor</u> 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 × 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*

Please see accompanying full Prescribing Information, including ***BOXED WARNING*** *for hepatotoxicity and teratogenicity.*

Contraceptive options for Females of Reproductive Potential

All Females of Reproductive Potential must use reliable contraception during Tracleer® treatment and for one month after stopping treatment. They should also have contraceptive counseling with either the prescriber or another designated healthcare provider trained in contraceptive counseling. Please refer to the table below for a complete list of acceptable contraceptive methods. A similar table can be found in the *Tracleer REMS Guide for Patients* and should be used to discuss acceptable birth control options with patients. The patient should be instructed to select one of the options listed below.

Acceptable birth control options

Option 1	or	Option 2	or	Option 3	or	Option 4
One method from this list:		**One method from this list:**		**One method from this list:**		**One method from this list:**
Standard intrauterine device (Copper T 380A IUD)		Estrogen and progesterone oral contraceptives ("the pill")		Diaphragm with spermicide		Partner's vasectomy
Intrauterine system (LNg 20 IUS: progesterone IUS)		Estrogen and progesterone transdermal patch		Cervical cap with spermicide		**PLUS One method from this list:**
Tubal sterilization		Vaginal ring		**PLUS One method from this list:**		Male condom
		Progesterone injection		Male condom		Diaphragm with spermicide
		Progesterone implant				Cervical cap with spermicide
		PLUS One method from this list:				Estrogen and progesterone oral contraceptives ("the pill")
		Male condom				Estrogen and progesterone transdermal patch
		Diaphragm with spermicide				Vaginal ring
		Cervical cap with spermicide				Progesterone injection
						Progesterone implant

- Educate and counsel females of reproductive potential about medical options in the event of unprotected sex or known or suspected contraceptive failure
- Remind patients to report if they miss a period or any other reason of suspected pregnancy during treatment to you immediately
- If pregnancy is suspected for any reason, a pregnancy test must be performed
- The prescriber must notify Actelion at 1-866-228-3546 of any pregnancies that occur during treatment or within 1 month of discontinuation

Please see accompanying full Prescribing Information, including ***BOXED WARNING*** *for hepatotoxicity and teratogenicity.*

Certified Pharmacies

Due to the risk of hepatotoxicity and teratogenicity, Tracleer® is only available through a network of certified pharmacies. For a list of certified pharmacies please call *Actelion Pathways*® at 1-866-228-3546.

Actelion Pathways is Actelion's services and support program that administers the Tracleer REMS Program.

OUTPATIENT PHARMACY CERTIFICATION:

Only a limited number of certified pharmacies will dispense Tracleer for outpatients. Prior to dispensing Tracleer to any patient, the pharmacy will confirm that the patient and the prescriber who wrote the prescription 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 during treatment with Tracleer

For all female patients of reproductive potential, the pharmacy will:

- Ask 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, pharmacies 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 into the Tracleer REMS program, the inpatient pharmacy agrees to:

- Complete training in the Tracleer REMS Program by reading the Tracleer Prescribing Information, *Tracleer 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 Pharmaceuticals US, Inc. ("Actelion") or FDA if any patient becomes pregnant 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 audited 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 for a specific inpatient while initiating enrollment.

To learn more about the serious risks associated with Tracleer, please refer to the full Prescribing Information including BOXED WARNING, the *Tracleer Medication Guide*, the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*, and the *Tracleer REMS Guide for Patients*. These materials are available at www.TracleerREMS.com.

If you have questions about Tracleer REMS Program enrollment, or if you would like more information about Tracleer, you can reach *Actelion Pathways* by calling toll-free at 1-866-ACTELION (1-866-228-3546).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

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ACTELION Pathways®

The Tracleer REMS Program is administered by *Actelion Pathways*®.

You can reach *Actelion Pathways* by calling toll free 1-866-ACTELION (1-866-228-3546).

For more information about the Tracleer REMS Program, please visit www.TracleerREMS.com.

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Tracleer® BOSENTAN TABLETS