CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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REMS

Initial REMS Approval: 08/2009
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NDA 21290
NDA 209279

Tracleer® (bosentan)

Sponsor: Actelion Pharmaceuticals Ltd
Contact: Actelion Clinical Research Inc
1820 Chapel Avenue West
Cherry Hill, NJ 08002
[856-773-4300]

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 REMS Patient Enrollment and Consent Form*

iii. *Tracleer REMS Patient Enrollment and Consent Form - VA use*

iv. *Prescriber and Pharmacy Guide for the Tracleer REMS Program*

v. *Tracleer REMS Guide for Patients*

vi. *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

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 hepatoxicity 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 Pre-pubertal 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 hepatotoxicty

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.

Tracleer® REMS Prescriber Enrollment and Agreement Form

Complete and fax this form to *Actelion Pathways*® at 1-866-279-0669.

Contact *Actelion Pathways* via phone at 1-866-ACTELION (1-866-228-3546).

Prescriber Information (please print)

First name | MI | Last name

Email address | NPI # | ☐ MD ☐ DO ☐ PA ☐ NP Professional designation

In the event you are unavailable, is there another person we can contact on your behalf? ☐ Yes ☐ No
If yes, please indicate.

Name | Phone

Office Practice/Clinic Information (please print)

Primary

Office practice/Clinic name | Affiliated hospital

Specialty | Office contact name | Office contact phone

Office email address | Phone | Fax

Address | City

State | ZIP | ☐ Phone ☐ Fax ☐ Email Preferred method of contact

Secondary

Office practice/Clinic name | Affiliated hospital

Specialty | Office contact name | Office contact phone

Office email address | Phone | Fax

Address | City

State | ZIP | ☐ Phone ☐ Fax ☐ Email Preferred method of contact

Tracleer REMS Prescriber Agreement

By signing below, you signify your understanding of the risks of Tracleer treatment and your obligations as a Tracleer prescriber to educate your patients about the Tracleer REMS (Risk Evaluation and Mitigation Strategy) Program, monitor them appropriately, and report any adverse events, including hepatotoxicity, and any pregnancies to the Tracleer REMS Program.

Signature | Date

Tracleer REMS Prescriber Enrollment Requirements

Specifically, you attest to the following:

- I have read the Tracleer Prescribing Information, the *Tracleer Medication Guide*, and the *Prescriber and Pharmacy Guide for the Tracleer REMS Program* and agree to comply with the Tracleer REMS Program requirements
- I agree to enroll all patients into the Tracleer REMS Program
- I will:
  - Advise all patients that Tracleer is only available through a restricted distribution program called the Tracleer REMS Program
  - Counsel patients on the risk of hepatotoxicity and review the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients* with the patient
  - Order and review liver function tests (ALT/AST/bilirubin) prior to initiating treatment and monthly during treatment
  - Counsel patients to immediately contact their healthcare provider 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)
  - Determine the reproductive potential status of female patient using the definitions provided in the *Prescriber and Pharmacy Guide for the Tracleer REMS Program*
  - Order and review pregnancy tests for Females of Reproductive Potential prior to initiating treatment with Tracleer, monthly during treatment, and for one month after stopping treatment
  - Counsel Females of Reproductive Potential (FRP) on the risks of Tracleer, including the risk of serious birth defects, and review the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients* with the patient
  - Counsel FRPs to use reliable contraception during Tracleer treatment, and for one month after stopping treatment; and discuss their medical options in the event of unprotected sexual intercourse or known or suspected contraceptive failure
  - Counsel FRPs to immediately contact their healthcare provider if they miss a menstrual period or suspect pregnancy
  - Counsel the Pre-pubertal Female patients and/or parent/guardian on the risks of Tracleer, including the risk of serious birth defects, and review the *Tracleer Medication Guide* with the patient and parent/guardian
  - Counsel Pre-pubertal Female patients and/or parent/guardian to immediately contact her healthcare provider if the patient begins to menstruate
  - Verify the reproductive potential status annually for Pre-pubertal Females who are at least 8 years of age and older by submitting a *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*
  - Report any change or misclassification in reproductive potential status by submitting a *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change
  - Counsel patients who fail to comply with the Tracleer REMS Program requirements
  - Notify Actelion of any adverse events, including hepatotoxicity, and report any pregnancies at 1-866-ACTELION (1-866-228-3546)

Please visit www.TracleerREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Tracleer REMS Program.

TRACLEER® REMS Patient Enrollment and Consent Form

Complete this form for ALL patients.
Fax this completed form to 1-866-279-0669.
Contact *Actelion Pathways*® at 1-866-228-3546 for questions.

ET3201604

1 Patient Information (please print)

First name | Middle initial | Last name | ☐ Male ☐ Female Gender

Birth date | Primary language | Email address

Primary phone # | Alternate phone # | Best time to call

Address | City | State | ZIP

Legal guardian | Relationship | Phone #

Emergency contact | Relationship | Phone #

2 Patient Agreement

For All Patients: I acknowledge that I understand that Tracleer is only available through a restricted distribution program under an FDA-required Risk Evaluation and Mitigation Strategy (REMS). I acknowledge that I have been counseled on the risks of Tracleer, including the risk of liver damage and serious birth defects. I have read the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients*. I understand that I will be contacted by Actelion, its agents, and/or a healthcare provider to receive counseling and education on the Tracleer REMS Program and the risks of Tracleer treatment to ensure that I am completing the required liver function tests before I start Tracleer and monthly before each refill. I agree to be counseled each month on the need for the monthly liver testing.

For Females Who Can Get Pregnant: I understand that I will be contacted by Actelion and/or its agents and contractors to receive counseling on the risk of serious birth defects, the need to use reliable contraception during Tracleer treatment and for one month after stopping Tracleer treatment, the importance of not becoming pregnant, and to ensure that I have completed pregnancy testing: before I start Tracleer, monthly before each refill, and for one month after stopping Tracleer. I agree to be counseled each month by the certified pharmacy on the need to use reliable contraception during Tracleer treatment and for one month after stopping Tracleer. I understand that I must immediately contact my healthcare provider if I miss a menstrual period or suspect that I am pregnant; and that I may be contacted by Actelion and/or its agents and contractors to obtain information about my pregnancy, if I become pregnant.

For Pre-pubertal Females: I acknowledge that I have received and read the *Tracleer Medication Guide* and that I understand that I must immediately contact my healthcare provider if I get my menstrual period.

For Post-menopausal Females: I acknowledge that I have received and read the *Tracleer Medication Guide*.

For Females with other medical reasons for permanent, irreversible infertility: I acknowledge that I have received and read the *Tracleer Medication Guide*.

★ **(REQUIRED)** Patient or Parent/Guardian Signature | Date

3 Prescriber Information (please print)

First name | Middle initial | Last name

Address | City | State | ZIP

Phone # | Fax #

NPI # | Tracleer Prescriber ID

Office contact and email address

4 Prescriber Authorization

For this patient, have you reviewed their liver function tests? ☐ Yes ☐ No

If your patient is FEMALE, check correct female patient category (please see definitions of these terms on the following page):

REQUIRED (Check one box)

Female of Reproductive Potential

If this patient is a Female of Reproductive Potential, has a negative pregnancy test been completed prior to prescribing Tracleer?

☐ Yes ☐ No

Female of Non-Reproductive Potential

☐ **Pre-pubertal Female** ☐ **Post-menopausal Female**

☐ **Female with other medical reasons for permanent, irreversible infertility**

I certify that the above therapy ordered is medically necessary and agree to follow the "Prescriber Requirements" indicated on the second page of this form. Further, I hereby authorize Actelion and/or its designated representative(s), to act on my behalf for the limited purposes of providing this prescription to the certified specialty pharmacy for patient treatment purposes.

★ **(REQUIRED FOR ALL PRESCRIBERS)** Prescriber Signature | Date

Reference ID: 4149548

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

Prescriber Requirements

For All Patients

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Tracleer® is only available through a restricted distribution program under an FDA-required REMS
- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Tracleer, including the risk of liver damage and serious birth defects, and that I have reviewed the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients* with the patient (and parent/guardian when appropriate)
- I will order and review liver function tests (ALT/AST/bilirubin) prior to initiation of treatment and monthly during treatment

For Females of Reproductive Potential

- I will order and review pregnancy tests prior to initiation of Tracleer treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Tracleer REMS Program
- I will evaluate the patient and agree to document any change or misclassification in reproductive potential status by submitting a *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

For Pre-pubertal Females

- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-pubertal Females who are at least 8 years of age and older, and agree to report any change or misclassification in reproductive potential status on a *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

5 Fax this form to 1-866-279-0669

Please visit www.TracleerREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Tracleer REMS Program.

TRACLEER® REMS Patient Enrollment and Consent Form

FOR VA USE ONLY

Complete this form for ALL patients.

Fax this completed form to 1-866-279-0669.

Contact *Actelion Pathways*® at 1-866-228-3546 for questions.

ET3201604

1 Patient Information (please print)

First name | Middle initial | Last name | ☐ Male ☐ Female Gender

Birth date | Primary language | Email address

Primary phone # | Alternate phone # | Best time to call

Address | City | State | ZIP

Legal guardian | Relationship | Phone #

Emergency contact | Relationship | Phone #

2 Patient Agreement

For All Patients: I acknowledge that I understand that Tracleer is only available through a restricted distribution program under an FDA-required Risk Evaluation and Mitigation Strategy (REMS). I acknowledge that I have been counseled on the risks of Tracleer, including the risk of liver damage and serious birth defects. I have read the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients*. I understand that I will be contacted by Actelion, its agents, and/or a healthcare provider to receive counseling and education on the Tracleer REMS Program and the risks of Tracleer treatment, to ensure that I am completing the required liver function tests before I start Tracleer and monthly before each refill. I agree to be counseled each month on the need for the monthly liver testing.

For Females Who Can Get Pregnant: I understand that I will be contacted by Actelion and/or its agents and contractors to receive counseling on the risk of serious birth defects, the need to use reliable contraception during Tracleer treatment and for one month after stopping Tracleer treatment, the importance of not becoming pregnant, and to ensure that I have completed pregnancy testing: before I start Tracleer, monthly before each refill, and for one month after stopping Tracleer. I agree to be counseled each month by the certified pharmacy on the need to use reliable contraception during Tracleer treatment and for one month after stopping Tracleer. I understand that I must immediately contact my healthcare provider if I miss a menstrual period or suspect that I am pregnant; and that I may be contacted by Actelion and/or its agents and contractors to obtain information about my pregnancy, if I become pregnant.

For Pre-pubertal Females: I acknowledge that I have received and read the *Tracleer Medication Guide* and that I understand that I must immediately contact my healthcare provider if I get my menstrual period.

For Post-menopausal Females: I acknowledge that I have received and read the *Tracleer Medication Guide*.

For Females with other medical reasons for permanent, irreversible infertility: I acknowledge that I have received and read the *Tracleer Medication Guide*.

★ **(REQUIRED)** Patient or Parent/Guardian Signature | Date

3 Prescriber Information (please print)

First name | Middle initial | Last name

Address | City | State | ZIP

Phone # | Fax #

NPI # | Tracleer Prescriber ID

Office contact and email address

4 VA Pharmacy Information (please print)

VA Pharmacy

Address | City | State | ZIP

Contact | Phone # | Fax #

5 Prescriber Authorization

For this patient, have you reviewed their liver function tests? ☐ Yes ☐ No

If your patient is FEMALE, check correct female patient category (please see definitions of these terms on the following page):

REQUIRED (Check one box)

Female of Reproductive Potential

If this patient is a Female of Reproductive Potential, has a negative pregnancy test been completed prior to prescribing Tracleer?

☐ Yes ☐ No

Female of Non-Reproductive Potential

☐ **Pre-pubertal Female** ☐ **Post-menopausal Female**

☐ **Female with other medical reasons for permanent, irreversible infertility**

I certify that the above therapy ordered is medically necessary and agree to follow the "Prescriber Requirements" indicated on the second page of this form. Further, I hereby authorize Actelion and/or its designated representative(s), to act on my behalf for the limited purposes of providing this prescription to the certified specialty pharmacy for patient treatment purposes.

★ **(REQUIRED FOR ALL PRESCRIBERS)** Prescriber Signature | Date

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

Prescriber Requirements

For All Patients

- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) that Tracleer® is only available through a restricted distribution program under an FDA-required REMS
- I acknowledge that I have counseled the patient (and parent/guardian when appropriate) on the risks of Tracleer, including the risk of liver damage and serious birth defects, and that I have reviewed the *Tracleer Medication Guide* and the *Tracleer REMS Guide for Patients* with the patient (and parent/guardian when appropriate)
- I will order and review liver function tests (ALT/AST/bilirubin) prior to initiation of treatment and monthly during treatment

For Females of Reproductive Potential

- I will order and review pregnancy tests prior to initiation of Tracleer treatment, monthly during treatment, and for 1 month after stopping treatment in accordance with the Tracleer REMS Program
- I will evaluate the patient and agree to document any change or misclassification in reproductive potential status by submitting a *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

For Pre-pubertal Females

- I will evaluate the patient's reproductive potential status, verify reproductive potential status annually for Pre-pubertal Females who are at least 8 years of age and older, and agree to report any change or misclassification in reproductive potential status on a *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form* within 10 business days of becoming aware of the change

6 Fax this form to 1-866-279-0669

Please visit www.TracleerREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Tracleer REMS Program.

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

Reference ID: 4149548

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 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.*

Reference ID: 4149548

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.*

Reference ID: 4149548

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

Reference ID: 4149548

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.

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

Reference ID: 4149548

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.

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

Tracleer® BOSENTAN TABLETS

ACTELION

TRACLEER® REMS (Risk Evaluation and Mitigation Strategy) Guide for Patients

Information to help you throughout your treatment with Tracleer

ACTELION Pathways®

Tracleer® BOSENTAN TABLETS

Reference ID: 4149548

Table of Contents

What is Tracleer?

Tracleer is a prescription medicine used to treat people with certain types of pulmonary arterial hypertension (PAH), which is high blood pressure in the vessels of the lungs.

Tracleer can improve your ability to exercise and can slow the worsening of your physical condition and symptoms. Tracleer lowers high blood pressure in your lungs and lets your heart pump more efficiently.

What are the serious risks of Tracleer?

Tracleer can cause **liver damage** and, if taken during pregnancy, can cause **serious birth defects**.

All patients—liver function must be monitored:

- When you start taking Tracleer,
- While taking Tracleer each month, and
- Any time your healthcare provider orders additional testing

Female patients—pregnancy must be avoided:

- When you start taking Tracleer,
- While taking Tracleer, and
- Within one month of stopping Tracleer

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 risk 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 **R**isk **E**valuation and **M**itigation **S**trategy.

How do I enroll in the Tracleer REMS Program?

There are several steps you must take:

1. Read this *Tracleer REMS Guide for Patients* and the *Tracleer Medication Guide* (which comes with your medicine)
2. Ask your healthcare provider any questions you have about taking Tracleer and the Tracleer REMS Program
3. Make sure you understand:
   - The benefits and risks of Tracleer
   - How to enroll and take part in the Tracleer REMS Program
4. Complete and sign the *Tracleer REMS 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

What are the Tracleer® REMS Program requirements for me?

- All patients need to have liver function tests prior to starting treatment and each month for as long as you are being treated with Tracleer. Your healthcare provider will order the liver function tests for you
- Go for any additional liver tests your healthcare provider orders for you. Your healthcare provider will monitor your liver function monthly and may adjust or stop your treatment if there are signs of liver damage
- Tell your healthcare provider if you have had liver problems, including liver problems while on other medicines
- Call your healthcare provider right away if you have any of these symptoms of liver problems while you are on Tracleer:
  - Nausea, vomiting, fever, unusual tiredness, stomach area (abdominal) pain, or yellowing of the skin or the whites of your eyes (jaundice)
- Females who can get pregnant must have a negative pregnancy test before starting Tracleer, each month while taking Tracleer, and for one month after stopping Tracleer. Your healthcare provider will order the pregnancy tests for you
  - You are considered a female who can get pregnant if you:
    - Have entered puberty, even if you have not started your period, and
    - Have a uterus, and
    - Have not gone through menopause (have not had a period for at least 12 months for natural reasons, or have had your ovaries removed)
- Females who can get pregnant must use reliable birth control at all times when taking Tracleer and for one month after stopping Tracleer. Your birth control options are listed on page 6
- Do not have unprotected sex
- Talk to your healthcare provider right away if you have unprotected sex, if you think your birth control has failed, or if you think you are pregnant. If so, your healthcare provider may discuss medical options with you (e.g., emergency contraception). Do not wait until your next appointment to tell your healthcare provider if you miss your menstrual period or if you think you are pregnant
- Tracleer is not available at your local pharmacy. You must receive Tracleer through a certified pharmacy (sometimes called a specialty pharmacy)
  - Your pharmacy will call you every month to ask if you have completed the liver function tests and pregnancy test (for females who can get pregnant) before shipping your Tracleer to your home or another shipping address you choose
  - You may not receive your Tracleer refill on time if you do not confirm with the pharmacy that you have had your monthly liver test or pregnancy test (for females who can get pregnant)

What are my birth control options?

Your healthcare provider will talk with you about your birth control options before starting Tracleer®. Ask your healthcare provider if you have any questions. Tell your healthcare provider if you want to change your birth control.

You must choose one of the 4 options listed below. More than one birth control method might be needed every time you have sex.

Acceptable birth control options

Option 1		Option 2		Option 3		Option 4
One method from this list:	**or**	**One method from this list:**	**or**	**One method from this list:**	**or**	**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

How will I receive Tracleer?

Tracleer is available only through certified pharmacies (also called specialty pharmacies).

- *Actelion Pathways*® provides support and services that help patients with their PAH medicines. Once you are enrolled, a Patient Case Manager will work with you to get your Tracleer prescription filled by a pharmacy
- Before your first prescription is filled, the pharmacy will call you to schedule a shipment of Tracleer that will come right to your home
- The *Tracleer Medication Guide* will be included in the package
- Read the *Tracleer Medication Guide* each time you receive it. Important information may have been added or changed

For a list of certified pharmacies, please call *Actelion Pathways* at **1-866-ACTELION (1-866-228-3546)**.

Reference ID: 4149548

Your steps to treatment with Tracleer®

Use this helpful checklist to get started with Tracleer and to stay on track during your treatment.

FIRST:

- ☐ Review the *Tracleer REMS Guide for Patients* and the *Tracleer Medication Guide* with your healthcare provider
- ☐ Make sure you understand the risks and benefits of taking Tracleer
- ☐ Tell your healthcare provider if you have had liver problems, including liver problems while taking other medicines
- ☐ Go for your liver function tests and pregnancy test (for females who can get pregnant)
- ☐ Enroll in the Tracleer REMS Program

NEXT:

- ☐ Expect a call from your Patient Case Manager. He or she will help you get your Tracleer prescription filled by one of the certified pharmacies
- ☐ Expect a call from the pharmacy to schedule your first shipment

EVERY MONTH: All Patients

- ☐ Read the *Tracleer Medication Guide* that comes with every shipment
- ☐ Complete the monthly liver function tests ordered by your healthcare provider
- ☐ Expect your pharmacy to call you every month to ask if you had your liver function tests in the last month before it reorders your Tracleer. The refill may not be done on time if you have not had your liver test
- ☐ Tell your healthcare provider right away if you have any of these symptoms of liver problems while taking Tracleer: nausea, vomiting, fever, unusual tiredness, stomach area (abdominal) pain, or yellowing of the skin or the whites of your eyes (jaundice)

EVERY MONTH: Female Patients who can get pregnant

- ☐ For female patients who can get pregnant, use the reliable birth control method(s) agreed upon with your healthcare provider — during treatment and for one month after you stop taking Tracleer
- ☐ Complete the monthly pregnancy test ordered by your healthcare provider
- ☐ Expect your pharmacy to call you every month to ask if you had a pregnancy test in the last month before it reorders your Tracleer. The refill may not be done on time if you have not had your pregnancy test
- ☐ Do not get pregnant. Tell your healthcare provider right away if you:
  - – Had unprotected sex
  - – Think that your birth control failed
  - – Miss a menstrual period
  - – Think you are pregnant

ACTELION Pathways®

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

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

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

*Please see accompanying full Prescribing Information, including **BOXED WARNING** for liver damage and birth defects, and Medication Guide.*

Tracleer® BOSENTAN TABLETS

ACTELION

Reference ID: 4149548

Tracleer® REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form

NOTE: THIS FORM SHOULD NOT BE USED TOGETHER WITH THE ENROLLMENT FORM.
USE IT ONLY TO REPORT A CHANGE IN REPRODUCTIVE STATUS OR FOR PRE-PUBERTAL ANNUAL VERIFICATION.

Complete this form to:

1) Change the reproductive status of any female patient within 10 business days of awareness of the change in reproductive status

2) Complete the annual verification of the reproductive potential status for Pre-pubertal Females 8 years of age or older

Fax this form to *Actelion Pathways*® at 1-866-279-0669.

Prescriber must complete this form within 10 business days of awareness of the change in reproductive status.

Patient Information (please print)

Patient Tracleer ID

First name | MI | Last name

Address

City | State | ZIP

Birth date | Phone

Prescriber Information (please print)

First name | MI | Last name

NPI #

Address

City | State | ZIP

Phone | Fax

Tracleer Prescriber ID (if available)

Office contact and email address (optional)

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

Select the most appropriate reason for submitting this form.

(For reference, please see the Definitions of Reproductive Potential Status)

Change in Status

- **Based on definitions of reproductive potential status, patient is (please check one):**
  - ☐ Female of Reproductive Potential
  - ☐ Female of Non-Reproductive Potential—Patient is pre-pubertal
  - ☐ Female of Non-Reproductive Potential—Patient is post-menopausal
  - ☐ Female of Non-Reproductive Potential—Other medical reasons for permanent, irreversible infertility
- **Reason for change in classification (please check one):**
  - ☐ Physiological transition
  - ☐ Medical/surgical (please specify): _____
  - ☐ Other (please specify): _____
- **Annual Verification**
  - ☐ Patient remains a Pre-Pubertal Female (8 years of age or older)

Prescriber acknowledgement (REQUIRED)

By signing, I certify that the patient's reproductive status as noted above is accurate, and that I will comply with the REMS requirements for my patient's reproductive potential status.

Prescriber signature | Title (MD/PA/NP, etc) | Date

Please visit www.TracleerREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Tracleer REMS Program.

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Reference ID: 4149548

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):

- In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness 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.

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

Materials for Prescribers

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

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*

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

Tracleer REMS Program Overview

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 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. 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 REMS Patient Enrollment and Consent Form*
- *Tracleer REMS Patient Enrollment and Consent Form for VA use*
- *Tracleer REMS Change in Reproductive Potential Status and Pre-pubertal Annual Verification Form*

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*

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 REMS 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

ACTELION

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

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

Materials for Prescribers

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

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*

Tracleer® REMS Inpatient Pharmacy Enrollment Form

Complete and fax this form to *Actelion Pathways*® at 1-866-279-0669.

You can also reach *Actelion Pathways* via phone at 1-866-ACTELION (1-866-228-3546).

Due to the risk of hepatotoxicity and teratogenicity, Tracleer is available only through a restricted program called the Tracleer REMS (Risk Evaluation and Mitigation Strategy) Program. In order for inpatients to receive Tracleer, all patients, as well as inpatient pharmacies that wish to stock this product, must enroll in the Tracleer REMS Program and agree to comply with the requirements of the program. An Authorized Representative must complete and submit this form on behalf of the inpatient pharmacy.

Inpatient Pharmacy Information (please print)

Name

☐ Hospital ☐ Nursing home ☐ Hospice ☐ Asylum/Mental facility ☐ Assisted Living ☐ Prison ☐ Rehabilitation

☐ Other (please specify): _____

Identification (please complete one of the following):

☐ Health Industry Number (HIN #) _____ ☐ National Provider Identifier (NPI #) _____

☐ Other identifier: _____

Address

City | State | ZIP

Phone # | Fax #

Ship To Address (if different from above)

Address

City | State | ZIP

Phone # | Fax #

Authorized Representative Information (please print)

Title:

☐ Hospital pharmacist ☐ Head of Pharmacy and Therapeutics (P&T) committee

☐ Other title: _____

Name

Authorized Representative phone # | Fax #

Authorized Representative email

Authorized Representative Consent

This inpatient pharmacy will:

- Put processes and procedures in place to ensure the Tracleer REMS Program 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 in a child-resistant container upon discharge of any patient
- Notify Actelion Pharmaceuticals US, Inc. (“Actelion”) or FDA of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer
- 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

I attest that I have read the Tracleer Prescribing Information, *Medication Guide*, and the *Prescriber and Pharmacy Guide for the Tracleer REMS Program* available at www.TracleerREMS.com.

I will ensure training of dispensing staff on the Tracleer REMS Program procedures and materials, including the *Prescriber and Pharmacy Guide for the Tracleer REMS Program* prior to dispensing Tracleer.

I agree that this pharmacy may be audited by the FDA, Actelion, or a designated third party.

Note: If your inpatient pharmacy needs Tracleer and is not enrolled in the Tracleer REMS Program, 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 of the pharmacy.

Signature | Date

Please visit www.TracleerREMS.com or call 1-866-ACTELION (1-866-228-3546) for more information about the Tracleer REMS Program.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
09/05/2017