NEW SUPPLEMENT FOR NDA 21-290

Tracleer (bosentan)
Actelion Clinical Research, Inc.
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Risk Evaluation Mitigation Strategy (REMS)
REMS MODIFICATION

November 15, 2012

Document No: D-12.636

I. GOAL(S)

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

1. To enable informed risk-benefit decisions for treating patients with Tracleer.
2. To minimize the risk of hepatotoxicity in patients who are exposed to Tracleer.
3. To minimize the risk of fetal exposures in female patients who are exposed to Tracleer.
4. To educate prescribers, patients, hospitals, and pharmacies on the safe-use conditions for Tracleer.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each Tracleer prescription and in accordance with 21 CFR 208.24.

B. Elements to Assure Safe Use

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

vi. Has educated and counseled any FCBP about the need to use reliable methods of contraception during treatment with Tracleer and for one month after treatment discontinuation

vii. Will notify Actelion of any adverse events, including hepatotoxicity, and to report any pregnancy during treatment with Tracleer

viii. Will counsel patients who fail to comply with program requirements

ix. For patients continuing therapy, will re-enroll patients into the REMS program after the first 12 months of treatment then annually thereafter

b. Actelion will

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

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

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

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

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

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

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

available on the Tracleer REMS website for 1 year from the date of the mailing.

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

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

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

   a. Outpatient Dispensing -

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

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

      ii. Counsel patients

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

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

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

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

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

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

vii. Provide a Medication Guide and Monthly Reminder Wallet card to patients each time Tracleer is dispensed

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

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

1. Obtain confirmation from the patient that the testing was completed.
2. If unable to obtain confirmation from the patient that the testing was completed, or if the patient cannot be reached, obtain confirmation from the patient's prescriber.
3. If the patient's prescriber cannot confirm that the required testing was completed, the certified pharmacy will:
    a. Remind the prescriber of his/her obligation to order and review monthly liver function tests and pregnancy tests (for FCBP)
    b. Ask the prescriber whether or not he/she authorizes the refill of Tracleer. The patient is eligible to receive a 30-day supply of Tracleer only if the prescriber authorizes the refill of Tracleer.

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

1. The certified pharmacy is notified by an enrolled patient and/or certified prescriber of the need to fulfill a greater than 30-day supply due to the patient's extended travel outside the US.
2. The certified pharmacy contacts the patient and the prescriber to verify the need. The certified pharmacy explains the process to the patient, and tells them that the form (FRM-549-COP-US) will be sent to the certified prescriber for completion and submission.
3. The certified pharmacy provides the prescriber with a letter explaining the process, and the request form (FRM-549-COP-US).

4. The certified prescriber completes the form and faxes it to the certified pharmacy.
5. The certified pharmacy reviews the form for completeness and contacts either the certified prescriber or the patient to obtain any additional information.
6. The medication is shipped to the patient, along with the Medication Guide and the required patient information sheet.
7. The certified pharmacy documents in their data management system that the patient met the criteria for the greater than 30-day supply due to foreign travel. This information is sent to Actelion as usual with the dispensed amount (in tablets), dose, and frequency captured.
8. The certified pharmacy contacts the prescriber for the monthly call in this situation to determine if safe-use conditions are being followed by the patient and prescriber. This is documented in the certified pharmacy data management system.

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

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

xiii. Agree to collect and report to Actelion specific data requirements needed to ensure compliance with the Tracleer REMS program including shipment records for every time Tracleer is dispensed. Actelion maintains the data in the T.A.P. database.

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

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

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

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

- Prescriber letter from certified pharmacy (accompanies FRM-549-COP-US)
- Patient Information Sheet (to be provided to the patient by the certified pharmacy)

b. Inpatient Dispensing -

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

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

1. The hospital will establish systems, order sets, protocols, or other measures to limit the use of Tracleer as outlined below and to ensure appropriate liver function and pregnancy tests are performed.
2. Tracleer will only be dispensed to inpatients who are under the supervision and care of a healthcare provider who has been certified in the Tracleer Access Program.
3. Tracleer will only be dispensed to inpatients who are already enrolled in the Tracleer Access Program or who will be enrolled prior to discharge from this hospital.
4. The hospital will dispense no more than a seven (7) day supply of Tracleer in a child-resistant container upon discharge of the patient.
5. A Tracleer Medication Guide will be provided to the patient prior to discharge from this hospital. (Available for download at www.TRACLEERREMS.com)
6. The hospital agrees to report adverse reactions to Actelion Pharmaceuticals US, Inc., including hepatotoxicity, and to report any pregnancy during treatment with Tracleer.
7. The hospital agrees to re-certify every three (3) years.
8. The hospital agrees to develop a system to track its compliance with the conditions above and provide information about its compliance to Actelion and/or the Food and Drug Administration upon request.

ii. Actelion will ensure that within 60 (sixty) days of the modified REMS approval, a Dear Hospital Letter will be sent. The target audience for the letter will be pharmacy directors at hospitals who have a history of dispensing Tracleer or who have a known affiliation with healthcare providers who specialize in the treatment of pulmonary arterial hypertension as identified via a national patient organization. The letter will explain the new requirement for hospital certification for inpatient use of Tracleer and the availability of the blister package for unit dosing. The letter will also be available on the Tracleer REMS website for 1 year from the date of the mailing.

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

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

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

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

- Tracleer Access Program Hospital Certification Form
- Dear Hospital Letter

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

   a. Actelion will ensure that patients treated with Tracleer are enrolled in the REMS program and assigned a unique identifying number before Tracleer is dispensed to him or her in the outpatient setting. Actelion will ensure that to become enrolled each patient consents to participate in the program for as long as they are taking the medication by acknowledging that he or she:

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

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

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

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

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

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

- Patient Essentials Guide
- Monthly Reminder Wallet Card

C. Implementation System

The Implementation System includes the following:

1. Actelion will maintain a database capturing certified prescribers, certified pharmacies, certified wholesale pharmacies, certified hospitals and enrolled patients.
2. Actelion will monitor distribution and prescription data to ensure that only certified pharmacies are distributing and dispensing Tracleer. The certified pharmacies are the only distributors of Tracleer.
3. Actelion will audit all certified pharmacies against their formal procedures and contractual arrangements at least once every 12 months and more frequently if non-compliance issues are identified.
4. Actelion will ensure that the certified pharmacies follow an agreed upon, scripted process to follow when a patient is identified as non-compliant with the testing, or the compliance with the required testing is uncertain in the previous month. The scripted process includes steps whereby the pharmacy provides prompt feedback to the prescriber on the potential non-compliance circumstances and reminds the prescriber of the need for ongoing monitoring. The pharmacies record their actions, and notify T.A.P.
5. Actelion will collect information from the certified pharmacies about compliance with hepatic and pregnancy testing and monitor the data in the T.A.P. database.
6. Actelion will evaluate certified hospitals who dispense Tracleer in the inpatient setting at least once every twelve (12) months and more frequently if non-compliance issues are identified.

D. Timetable for Submission of Assessments

Actelion will submit REMS assessments to FDA annually on January 19th. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Actelion will submit each assessment so that it will be received by the FDA on or before the due date.

Tracleer® (bosentan) Enrollment for Patients and Prescribers

Please complete and fax this form and copies of all insurance cards to PAH Pathways® at 1-866-279-0669. The information will be entered into the Tracleer Access Program (T.A.P.®) database and forwarded to a certified specialty pharmacy for follow-up with you as needed. Please contact PAH Pathways at 1-866-228-3546 for questions.

Patient Information

First name:	MI:	Last name:	Gender: ☐ Male ☐ Female
SSN:		DOB:	Primary language:
E-mail address:	Phone #:	Alternate Phone #:	Best time to call:
Address:		City:	State: / ZIP:
Legal guardian/emergency contact:		Relationship:	Phone #:
Shipping directions: ☐ Physician office ☐ Patient's home		Shipping attn:	
Shipping address:		City:	State: / ZIP:

Insurance Information

Insurance Company (Primary or Prescription Coverage):		Phone #:
Name of insured:	Policy #:	Group/Policy #:
Indicate specialty pharmacy preference:	If left blank, this referral will be sent to the appropriate specialty pharmacy based on the patient's existing benefits.	

I have read and agreed to the Patient Agreement on the back of this form. I have reviewed the Medication Guide with my prescriber, I consent to be enrolled in the Tracleer Access Program, and I agree to comply with the program for as long as I am prescribed Tracleer.

Patient/guardian signature: _____ Date: _____

Prescriber and Prescription Information

First name:	MI:	Last name:	E-mail Address:	Degree:
DEA #:	NPI #:	Tax ID #:	State license #:	

Complete section below only if you are a new prescriber or your contact information has changed.

Facility name:	Affiliated hospital:	Specialty:	
Office contact:	E-mail Address:	Phone #:	Fax #:
Primary address:	City: / State: / ZIP:	Preferred method of contact: ☐ Phone ☐ Fax ☐ E-mail	

DIAGNOSIS (CHECK Only One Box for the Diagnosis Related to Tracleer Treatment):

ICD 416.0 – Pulmonary Arterial Hypertension (PAH)
☐ Idiopathic PAH ☐ Familial PAH

OR

ICD 416.8 – Pulmonary Arterial Hypertension
☐ Connective tissue disease ☐ Congenital heart disease ☐ Other _____

BEFORE SIGNING, SEE IMPORTANT SAFETY INFORMATION ON BACK.
REQUIRED: Please complete all sections below:

1. You have reviewed liver function tests. ☐ Yes ☐ No
2. Patient is a female of childbearing potential? ☐ Yes ☐ No
3. If #2 is yes, you have confirmed a negative pregnancy test. ☐ Yes ☐ No
4. Is patient currently in an inpatient facility? ☐ Yes ☐ No
5. Directions for Use and Dispensing Instructions: Complete A or B below
   A. ☐ Sig: Take 62.5 mg tablet by mouth twice daily × 4 weeks, then increase to the maintenance dose of 125 mg tablet by mouth twice daily.
   Disp: Tracleer 62.5 mg tablets (66215-0101-06) (60 tablets). No refills.
   Tracleer 125 mg tablets (66215-0102-06) (60 tablets). Refill × 11.

   OR

   B. ☐ Sig: _____
   _____
   Disp: Tracleer 62.5 mg tablets (66215-0101-06) _____(Qty) tablets
   Tracleer 125 mg tablets (66215-0102-06) _____(Qty) tablets
6. **By signing, I certify that the above therapy is medically necessary. If shipped to prescriber's office, prescriber accepts on behalf of patient.**

Prescriber attestation: _____ Date: _____

Prescriber Certification: Complete this section only if you are not currently a certified prescriber. My signature below certifies that:

1. I have read and understood the communication and educational materials for prescribers regarding the risks of Tracleer, and agree to document that I:
   – Reviewed and discussed the Medication Guide and the risks of Tracleer (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   – Reviewed liver function tests (ALT/AST/bilirubin) and confirmed that my patients are not pregnant (if applicable), and I agree to order and monitor monthly liver function tests and, if applicable, pregnancy tests.
   – Educated and counseled females of childbearing potential **(see definition on reverse side)** to notify me if they suspect they may be pregnant.
   – Educated and counseled females of childbearing potential about the need to use reliable methods of contraception **(see table on reverse side)** during treatment with Tracleer and for one month after treatment discontinuation.
2. I will notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer.
3. I will counsel my patients who fail to comply with the program requirements.
4. I will renew my patients' T.A.P. enrollment annually by completing and submitting a new form for patients continuing therapy.

Prescriber signature: _____ Date: _____

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Tracleer® (bosentan) Enrollment for Patients and Prescribers

PO Box 826, South San Francisco, CA 94083-0826 • Phone 1-866-ACTELION (1-866-228-3546) or Fax 1-866-279-0669 -

Patient Agreement

- I have reviewed the Medication Guide with my healthcare provider. I understand that a Medication Guide will be provided to me each time I receive a prescription for Tracleer, and that I must read it each time because it may have new information important to my treatment.
- I have been informed of the risks of treatment with Tracleer, including the risks of liver damage and birth defects. I understand that I will be contacted by Actelion, its agents, and/or a healthcare provider to receive counseling on the risks of Tracleer treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for females of childbearing potential—see definition below) and, if I am a female who becomes pregnant, to obtain information about my pregnancy.
- I agree to notify Actelion or my specialty pharmacy if I should change prescribers.
- I agree to have monthly blood tests as ordered by my healthcare provider for as long as I take Tracleer.
- I authorize my healthcare providers, health plans, other payers, and pharmacies to disclose my personal, medical, and health information to Actelion Pharmaceuticals US, Inc., and its employees, distributors, agents, and contractors ("Actelion"), and I authorize Actelion to use and disclose this information for use in implementing T.A.P. including to: 1) establish my benefit eligibility; 2) communicate with my healthcare providers, health plans, other payers, and pharmacies about my medical care; 3) provide support services, including facilitating the provision of Tracleer to me; and 4) help find ways to pay for Tracleer, or for treatment or healthcare operations in progress.
- I understand that Actelion cannot guarantee that it will be able to find ways to pay for my Tracleer, and I know that I am responsible for the costs of my care.
- I understand that I may be contacted by Actelion or its delegates regarding important safety surveys while I am taking Tracleer.
- I understand that once my health information has been disclosed to Actelion, privacy laws may no longer restrict its use or disclosure; however, Actelion agrees to protect my information by using and disclosing it only for the purposes described above or as required by law.
- I acknowledge and agree that, although Actelion will have access to my personal health information, Actelion will not be providing counseling or medical advice regarding my condition. I further understand that all questions regarding my medical and health conditions should be discussed with my healthcare provider.
- I consent to be in the Tracleer Access Program for as long as I am taking Tracleer.

Definition of Female of Childbearing Potential (FCBP)

Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable methods of contraception during treatment with Tracleer

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

PRESCRIBER ESSENTIALS

Your guide to enrolling and renewing patients in the Tracleer Access Program (T.A.P.®)

Please see accompanying full prescribing information, including ***BOXED WARNING*** *about hepatotoxicity and teratogenicity.*

PAHPathways®
ACTELION SERVICES & SUPPORT

Tracleer Access Program (.

Tracleer®
BOSENTAN TABLETS

Introduction to the essentials

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO class II patients, which may preclude future use as their disease progresses.

Because of the risks of hepatotoxicity and teratogenicity, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.®), which is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, pharmacies, and hospitals must enroll in the program.

In order to receive Tracleer, hospitals, prescribers, and patients must enroll in T.A.P. and agree to comply with the requirements of the program. In addition, Tracleer is dispensed only through specialty pharmacies.

Program overview

Tracleer Access Program (T.A.P.)

Before you prescribe Tracleer, you must familiarize yourself with the content of this educational guide as well as the full prescribing information in the back pocket. In order to receive Tracleer, prescribers and patients must enroll in T.A.P. and agree to comply with the requirements of this program. Upon your first patient enrollment and annually thereafter, you must certify that you are aware of and have fulfilled essential steps that will help ensure the ongoing safe use of Tracleer. Prescriber certification may be completed using either the Tracleer Enrollment for Patients and Prescribers form or the separate Tracleer Prescriber Certification form.

As a certified prescriber of Tracleer, you may be contacted periodically to provide feedback regarding the effectiveness of T.A.P. to further ensure the ongoing safe use of Tracleer.

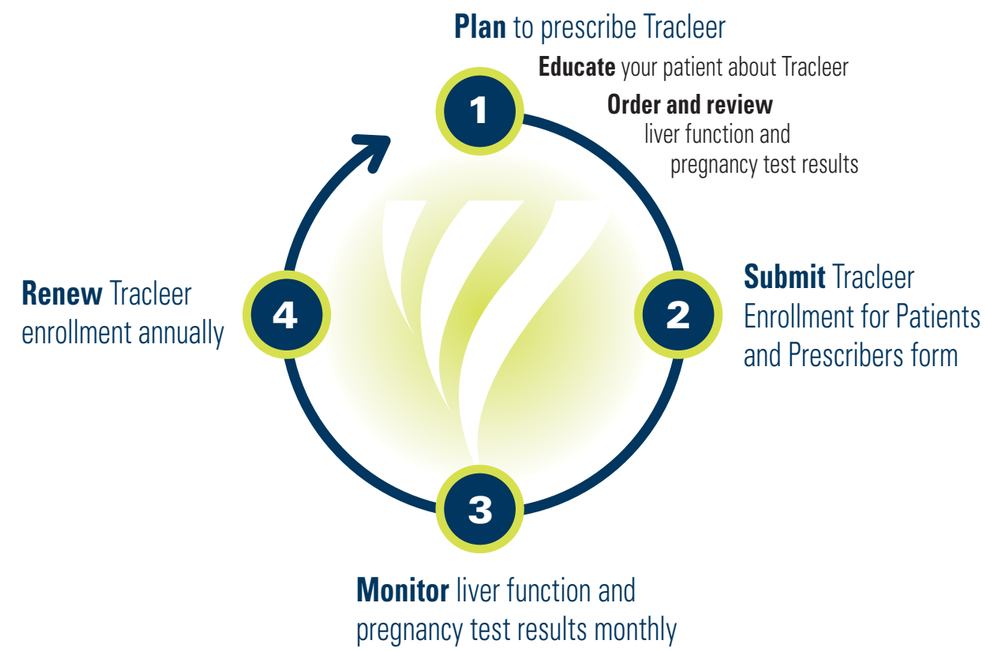
T.A.P. is administered by PAH Pathways®. You can reach PAH Pathways by calling toll-free at 1-866-ACTELION (1-866-228-3546). For more information about T.A.P. and the requirements of the program, please visit www.TracleerREMS.com.

Certified specialty pharmacies

Tracleer is not dispensed through retail pharmacies; rather, Tracleer is dispensed through a restricted network of certified specialty pharmacies. Specialty pharmacies help with patient management by confirming required monthly liver function and pregnancy testing. Specialty pharmacies also arrange for Tracleer to be delivered conveniently and directly to patients each month. If a patient does not confirm having the monthly tests or becomes pregnant, the pharmacy will contact you.

Reference ID: 3334175
Page 13

4 ESSENTIAL steps to enrollment and renewal



Tracleer® BOSENTAN TABLETS

1 Plan to prescribe Tracleer

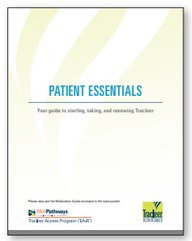
Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO class II patients, which may preclude future use as their disease progresses.

You must address and document (see step 2 on next page) these points with every Tracleer enrollment:

- Before prescribing Tracleer, review the Medication Guide and discuss the risks of treatment with your patients, including the risks of hepatotoxicity and teratogenicity.
- Order and review liver function tests (ALT/AST/bilirubin) and confirm that your female patients of childbearing potential are not pregnant. **See the definition of "Female of childbearing potential" on page 9.**
- Agree to order and monitor monthly liver function and, if applicable, pregnancy tests.
- Educate and counsel females of childbearing potential on the need to use reliable methods of contraception during treatment with Tracleer and for 1 month after treatment discontinuation. See the table "Reliable methods of contraception" on page 9.
- Educate and counsel females of childbearing potential to notify you if they suspect they may be pregnant.

You must also agree to:

- Counsel any patient who fails to comply with the program requirements
- Notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer
- Renew your patients' Tracleer enrollment annually by completing and submitting the Tracleer Renewal form

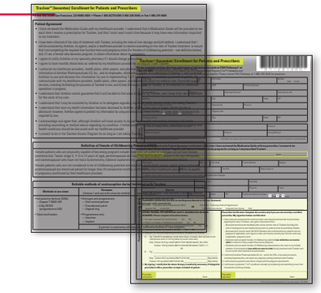


The Patient Essentials guide is available to help you discuss the steps of Tracleer enrollment and renewal with your patients. The Tracleer Medication Guide, which you must review with your patients prior to prescribing Tracleer, is included in its entirety in the back pocket of the Patient Essentials guide.

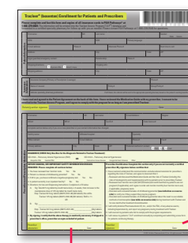
2 Submit Tracleer Enrollment for Patients and Prescribers form

To enroll your patients in T.A.P.® with each Tracleer Enrollment for Patients and Prescribers form you must:

- Read and complete it in its entirety
- Sign the Prescriber Certification (only if you are not currently a certified prescriber)
- Complete and sign the prescription information
- Document patient consent to the terms of the Tracleer Enrollment for Patients and Prescribers form
- Fax the form to 1-866-279-0669



Keep copies of all completed Tracleer Enrollment for Patients and Prescribers forms.



Prescriber Certification: Complete this section only if you are not currently a certified prescriber. My signature below certifies that:

1. I have read and understood the communication and educational materials for prescribers regarding the risks of Tracleer, and agree to document that I:
   - Reviewed and discussed the Medication Guide and the risks of Tracleer (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   - Reviewed liver function tests (ALT/AST/bilirubin) and confirmed that my patients are not pregnant (if applicable), and I agree to order and monitor monthly liver function tests and, if applicable, pregnancy tests.
   - Educated and counseled females of childbearing potential **(see definition on reverse side)** to notify me if they suspect they may be pregnant.
   - Educated and counseled females of childbearing potential about the need to use reliable methods of contraception **(see table on reverse side)** during treatment with Tracleer and for one month after treatment discontinuation.
2. I will notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer.
3. I will counsel my patients who fail to comply with the program requirements.
4. I will renew my patients' T.A.P. enrollment annually by completing and submitting a new form for patients continuing therapy.

Prescriber signature: _____ Date: _____

Prescriber Certification

BEFORE SIGNING, SEE IMPORTANT SAFETY INFORMATION ON BACK.
REQUIRED: Please complete all sections below:

1. You have reviewed liver function tests. ☐ Yes ☐ No
2. Patient is a female of childbearing potential? ☐ Yes ☐ No
3. If #2 is yes, you have confirmed a negative pregnancy test. ☐ Yes ☐ No
4. Is patient currently in an inpatient facility? ☐ Yes ☐ No
5. Directions for Use and Dispensing Instructions: Complete A or B below
   A. ☐ Sig: Take 62.5 mg tablet by mouth twice daily × 4 weeks, then increase to the maintenance dose of 125 mg tablet by mouth twice daily.
   Disp: Tracleer 62.5 mg tablets (66215-0101-06) (60 tablets). No refills.
   Tracleer 125 mg tablets (66215-0102-06) (60 tablets). Refill × 11.
   OR
   B. ☐ Sig: _____
   Disp: Tracleer 62.5 mg tablets (66215-0101-06) _____(Qty) tablets
   Tracleer 125 mg tablets (66215-0102-06) _____(Qty) tablets
6. **By signing, I certify that the above therapy is medically necessary. If shipped to prescriber's office, prescriber accepts on behalf of patient.**

Prescriber attestation: _____ Date: _____

Prescription Information

Tracleer® BOSENTAN TABLETS

Reference ID: 3334175
Page 14

3 Monitor liver function and pregnancy test results monthly

The use of Tracleer requires that you obtain and review monthly liver function and, if applicable, pregnancy tests. You must counsel your patients about the importance of monthly testing and ensure that test results are obtained and reviewed by your office. The specialty pharmacy will confirm with your patients that monthly tests have been obtained. If a patient does not confirm having the monthly tests or becomes pregnant, the pharmacy will contact you. Notify Actelion and/or the FDA of any pregnancies or adverse events, including hepatotoxicity, by calling toll-free at 1-866-ACTELION (1-866-228-3546).

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

Tracleer aminotransferase (ALT/AST) management[1]

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 test; **if confirmed, reduce the dose or interrupt** treatment and monitor LFT levels every 2 weeks **Continue or reintroduce† Tracleer** if levels return to pretreatment levels
>5 to ≤8 × ULN	**Confirm** by another test; if confirmed, stop therapy; monitor LFTs at least every 2 weeks **Consider** reintroduction† of therapy if LFTs return to pretreatment levels
>8 × ULN	**Stop** therapy; do not reintroduce

*Upper limit of normal.

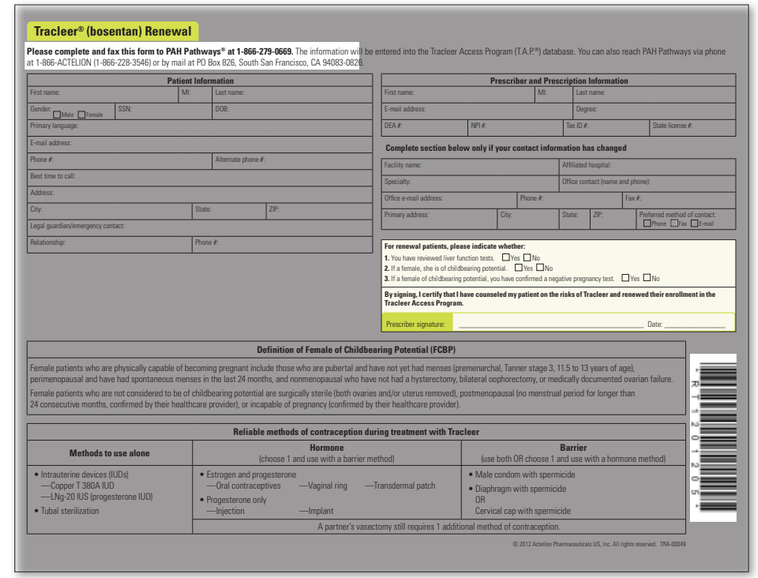
†If Tracleer is reintroduced it should be at the starting dose; aminotransferase levels should be checked within 3 days.

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*** *about hepatotoxicity and teratogenicity.*

4 Renew Tracleer enrollment annually

Annually, you must renew your patient in the Tracleer Access Program (T.A.P.®). By renewing your patients in T.A.P., you are agreeing that you have counseled them on the risks and benefits of Tracleer. You may renew your patient by completing the Tracleer Renewal form.



Tracleer® (bosentan) Renewal

Please complete and fax this form to PAH Pathways® at 1-866-279-0669. The information will be entered into the Tracleer Access Program (T.A.P.®) database. You can also reach PAH Pathways via phone at 1-866-ACTELION (1-866-228-3546) or by mail at PO Box 826, South San Francisco, CA 94083-0826.

Patient Information

First name: | MI: | Last name:
Gender ☐Male ☐Female | SSN: | DOB:
Primary language:
E-mail address:
Phone #: | Alternate phone #:
Best time to call:
Address:
City: | State: | ZIP:
Legal guardian/emergency contact:
Relationship: | Phone #:

Prescriber and Prescription Information

First name: | MI: | Last name:
E-mail address: | Degree:
DEA #: | NPI #: | Tax ID #: | State license #:

Complete section below only if your contact information has changed

Facility name: | Affiliated hospital:
Specialty: | Office contact (name and phone):
Office e-mail address: | Phone #: | Fax #:
Primary address: | City: | State: | ZIP: | Preferred method of contact: ☐Phone ☐Fax ☐E-mail

For renewal patients, please indicate whether:
1. You have reviewed liver function tests. ☐Yes ☐No
2. If a female, she is of childbearing potential. ☐Yes ☐No
3. If a female of childbearing potential, you have confirmed a negative pregnancy test. ☐Yes ☐No

By signing, I certify that I have counseled my patient on the risks of Tracleer and renewed their enrollment in the Tracleer Access Program.

Prescriber signature: _____ Date: _____

Definition of Female of Childbearing Potential (FCBP)

Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable methods of contraception during treatment with Tracleer

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Vaginal ring —Transdermal patch • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide

A partner's vasectomy still requires 1 additional method of contraception.

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Tracleer Renewal form

Tracleer® BOSENTAN TABLETS

Safety profile: Liver warnings

The following pages contain important safety information about treatment with Tracleer® (bosentan). You must be familiar with this information before prescribing Tracleer.

Tracleer may cause liver damage[1]

- In clinical studies, Tracleer caused at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases.
- After prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis were observed in a setting of close monitoring.
- Because these changes are a marker for potential serious hepatotoxicity, liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter.
- Elevations in aminotransferases require close attention. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.
- Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Liver enzyme elevations: experience and management

- Use of Tracleer should generally be avoided in patients with elevated aminotransferases (>3 × ULN) **at baseline** because monitoring for hepatotoxicity may be more difficult.[1]
- It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.[1]
  - 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.
- For treatment and monitoring recommendations, see the table on page 6.
  - For patients whose **monthly** LFTs are ≤3 × ULN, no change in monitoring schedule or dosage is required.[1]
  - For patients whose **monthly** LFTs are >3 × ULN, close monitoring and either dose reduction or treatment cessation are necessary.[1]

Please see accompanying full prescribing information, including ***BOXED WARNING*** *about hepatotoxicity and teratogenicity.*

Reference ID: 3334175
Page 16

Safety profile: Pregnancy warnings

Pregnancy must be excluded and prevented[1]

- Tracleer is very likely to cause major birth defects if used by pregnant females, based on animal data.
- To prevent pregnancy, females of childbearing potential must use 2 reliable methods of contraception during treatment and for 1 month after stopping Tracleer.
- Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives, should not be used as the sole means of contraception because they may not be effective in patients receiving Tracleer.
- Obtain monthly pregnancy tests.
- Please remember that a patient receiving Tracleer can transition into a female of childbearing potential during the course of therapy.

Female of childbearing potential[1]

- Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.
- Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable methods of contraception during treatment with Tracleer[1]

- Females of childbearing potential using Tracleer must use 2 reliable methods of contraception unless they have had a tubal sterilization or have a Copper T 380A IUD or LNg-20 IUS inserted.

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

Safety profile: Warnings, precautions, adverse events, and drug interactions

Safety profile when administered with other standard PAH medication in pivotal trials

- Patients receiving Tracleer continued other medications, including anticoagulants, digoxin, diuretics, and vasodilators such as calcium channel blockers and ACE inhibitors.[2,3]
- Patients receiving epoprostenol within 3 months of study screening were ineligible for participation.[2,3]
- In the EARLY trial, both the Tracleer group and the placebo group included some patients on sildenafil at baseline (Tracleer, n=14; placebo, n=15).[4]

Fluid retention[1]

- Peripheral edema is a known clinical consequence of PAH and worsening PAH, and is also a known effect of other endothelin receptor antagonists.
- In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7% (placebo-corrected) of patients.
- There have been postmarketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer.
- If clinically significant fluid retention develops, further evaluation should be undertaken to determine the cause, and the possible need for treatment or discontinuation of Tracleer therapy.

Pulmonary veno-occlusive disease (PVOD)[1]

- If signs of pulmonary edema occur when Tracleer is administered, consider the diagnosis of associated PVOD and consider discontinuing Tracleer.

Decreased sperm counts[1]

- In an open-label study (N=25), a decline in sperm count of at least 50% in 25% of Tracleer-treated patients was observed after 3 or 6 months. Sperm count remained in normal range after 6 months, with no changes in sperm morphology, sperm motility, or hormone levels.
- It cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Associated with dose-related decreases in hemoglobin[1]

- Decreases in hemoglobin concentration:
  - Measured 0.9 g/dL (overall mean decrease) for Tracleer-treated patients
  - Were detected during the first few weeks of treatment
  - Stabilized by 4 to 12 weeks of treatment
- Monitoring of hemoglobin concentrations recommended after 1 and 3 months, and quarterly thereafter

Please see accompanying full prescribing information for complete description of adverse events.

Adverse events[1]

Adverse events occurring in ≥3% of patients treated with Tracleer and more frequently than the placebo group*

Adverse Event	Tracleer (n=258)		Placebo (n=172)	
Respiratory tract infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Serum aminotransferases abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	-	-

*Investigator-reported safety data obtained from 430 patients in placebo-controlled trials in PAH at doses of 125 mg BID or 250 mg BID.

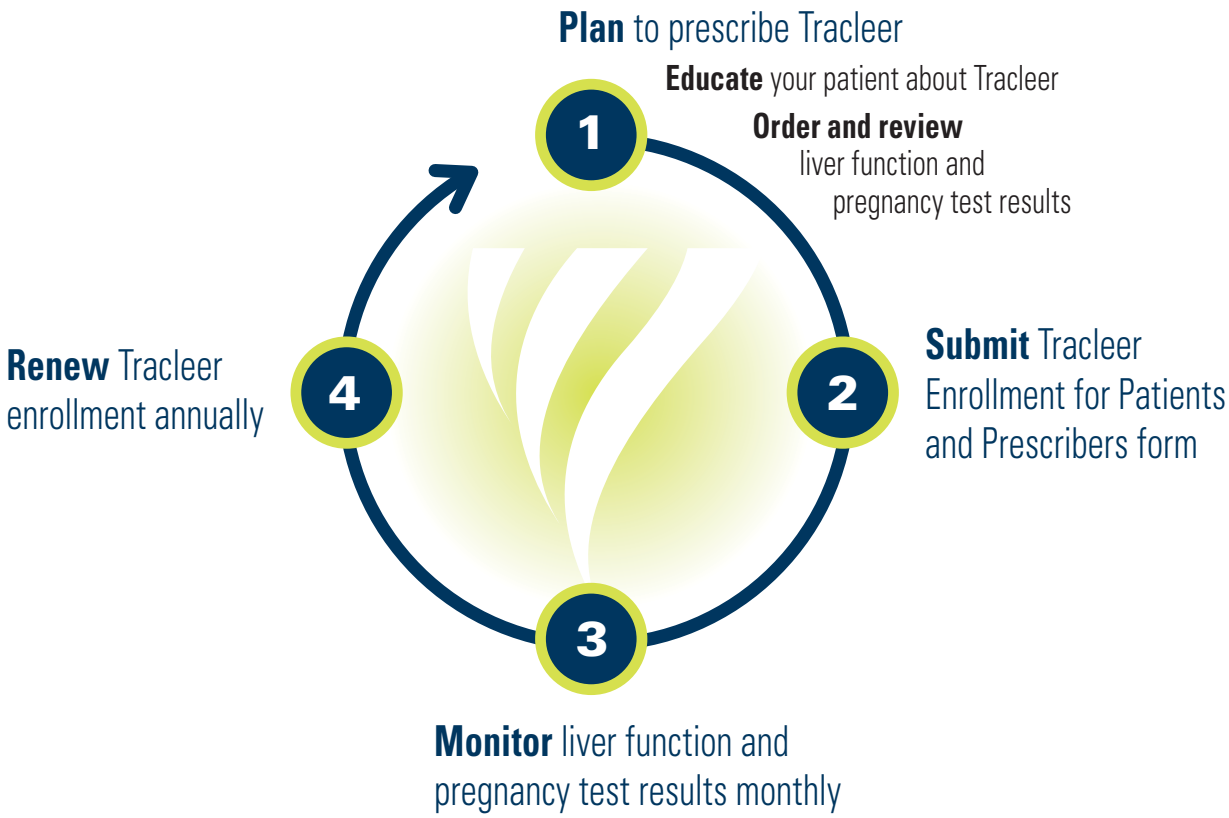
Drug interactions[1]

- Tracleer is contraindicated for use with cyclosporine A and glyburide.
- Tracleer is metabolized by CYP2C9 and CYP3A.
  - Co-administration with agents that are metabolized by these pathways may affect plasma concentrations of one or both agents.
  - When initiating lopinavir/ritonavir and other ritonavir-containing HIV regimens, dosage adjustment of Tracleer is necessary.
  - When co-administered with simvastatin, or other statins that are CYP3A substrates, dosage adjustment of such statins may need to be considered.
  - When co-administered with rifampicin, a CYP3A inducer, liver function should be monitored weekly for the first 4 weeks before reverting to normal monitoring.
  - Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals; caution should be exercised if they are used together.
  - When co-administered with ketoconazole, a potent CYP3A inhibitor, no dose adjustment of bosentan is necessary, but increased effects of Tracleer may need to be considered.
- There are no clinically relevant interactions between Tracleer and warfarin, digoxin, nimodipine, losartan, or sildenafil.
  - Dose adjustments are not necessary when Tracleer and sildenafil are co-administered.
- Tracleer has no significant interaction with iloprost.

1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. October 2012. **2.** Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903. **3.** Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001;358:1119-1123. **4.** Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet.* 2008;371:2093-2100.

Tracleer® BOSENTAN TABLETS

4 ESSENTIAL steps to success



If you have questions about Tracleer enrollment and renewal, or if you would like more information about Tracleer, you can reach PAH Pathways, which administers T.A.P., by calling toll-free at 1-866-ACTELION (1-866-228-3546).

Please see accompanying full prescribing information, including ***BOXED WARNING*** *about hepatotoxicity and teratogenicity.*

PAHPathways®
ACTELION SERVICES & SUPPORT

Tracleer Access Program (.

Tracleer
BOSENTAN TABLETS

ACTELION

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FRM-549-COP-US

30+ Day Request and Justification Form

To: Specialty Pharmacy (fax #)

Request Date: _____

PATIENT INFORMATION

Name (First & Last): _____

Patient Registration #: AC _____ Date of Birth (MM/DD/YYYY): _____

Has the patient completed a minimum of three (3) months therapy with normal liver and/or pregnancy test results? YES NO

PRESCRIBING PHYSICIAN INFORMATION

Name (First & Last): _____

Office Contact: _____ Office phone #: ( ) _____ - _____

I, _____ request a supply of Tracleer of

Name of prescribing physician

2 Months 3 Months (not to exceed 3 months) for the above named patient for the following reason:
Travel outside the United States

I agree to accept the responsibility for monitoring the patient's blood tests for LFT and Pregnancy (if a female of childbearing potential) and to make those records available if necessary.

X _____

Prescribing Physicians Signature

Dear Doctor _____

We have received your request for a greater than 30-day supply of Tracleer (bosentan) for Patient Name.

As you may be aware Tracleer is typically shipped as a 30-day supply shipment. This was done to permit assure monthly liver and pregnancy testing before each shipment.

The FDA has approved a process whereby you can submit a written request for a greater than 30-day supply of Tracleer. This request must meet certain criteria and MUST NOT be for more than a 90-day supply.

We remind you that monitoring liver function and pregnancy status on a monthly basis is required. If your patient meets the criteria and is dispensed a greater than 30-day supply to travel outside of the US, you will be contacted in their place each month to determine if liver function testing has been completed. If the patient is a female of child bearing potential, you will be asked to confirm that pregnancy testing has been completed and she is utilizing reliable methods of contraception.

Please complete the enclosed 30+ Day Supply Request and Justification Form and fax it back to us at Fax #. Please allow as much lead-time as possible for review and processing. We will notify you of the outcome.

If you have any questions about the process, timing, or documentation, please contact us at Specialty Pharmacy Phone #.

Sincerely,

Name

TRACLEER SUPPLY – PATIENT INFORMATION SHEET

ATTENTION

Based on a request from your prescriber , we are sending you more than a 30-day supply of Tracleer.

While you are traveling outside of the United States, it is critical that you obtain liver function and pregnancy testing (if you are a female of childbearing potential) EVERY 30 days and have those tests reviewed by your prescriber to assure the results are acceptable. The proof of the testing and the results of those tests should be communicated to your prescriber in the US.

Tracleer can cause liver damage. Therefore you must have a blood test to check your liver function before you start Tracleer and each month after that. See the "**What is the most important information I should know about Tracleer?**" section of the Tracleer Medication Guide for information about the symptoms of liver problems.

Tracleer can cause serious birth defects if taken during pregnancy. You must not be pregnant when you start taking Tracleer or during Tracleer treatment. Serious birth defects from Tracleer can happen early in pregnancy. Females who are able to get pregnant must have a negative pregnancy test before starting and each month during Tracleer treatment.

Failure to have the tests done, and the results reviewed, could lead to medical problems. By requesting and accepting this shipment containing more than a 30-day supply of Tracleer, you have agreed to obtain liver function and pregnancy tests every 30 days, have them reviewed by a healthcare provider, and have the test results promptly reported to your healthcare provider in the US.

A copy of the full Prescribing Information is included with this supply. Please give it to the healthcare provider who arranges for and reviews your liver and pregnancy tests so that he or she has information on Tracleer.

Should you have ANY medical concerns or experience any side effects, contact your healthcare provider immediately.

PATIENT ESSENTIALS

Your guide to starting, taking, and renewing Tracleer

Please also see the Medication Guide enclosed in the back pocket.

PAHPathways®
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Tracleer Access Program (.

Tracleer®
BOSENTAN TABLETS

Introduction to the essentials

This booklet describes how you and your healthcare provider will work together to ensure the safe use of Tracleer. Tracleer can cause liver damage, including rare cases of liver failure. Tracleer is very likely to cause serious birth defects if taken during pregnancy. Because of these risks, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.®), which is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Before you begin taking Tracleer, you must read and agree to all the instructions in T.A.P.

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 blood more efficiently.

Starting Treatment with Tracleer

To start treatment with Tracleer, you must:

- Review safety information with your healthcare provider
- Complete a Tracleer Enrollment for Patients and Prescribers form
- Agree to have important monthly tests

To continue therapy with Tracleer, you and your healthcare provider will renew your enrollment each year by completing the Tracleer Renewal form.

As a patient taking Tracleer, you may be contacted about your understanding of the risks with the use of Tracleer.

*Please see accompanying full prescribing information, including **BOXED WARNING** about liver damage and birth defects, and Medication Guide.*

Reference ID: 3334175
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What is the most important information I should know about Tracleer?

Tracleer is only available through the Tracleer Access Program (T.A.P.). Before you begin taking Tracleer, you must read and agree to all of the instructions in T.A.P.

Tracleer can cause serious side effects including:

Liver damage

- Liver damage may not cause symptoms at first. Only a blood test can show if you have early liver damage. You must have a blood test to check your liver function before you start Tracleer and each month after that. Your healthcare provider will order these tests. Regular blood tests are important because they will help your healthcare provider adjust or stop your treatment before there is permanent damage.
- Tell your healthcare provider if you have had liver problems, including liver problems while taking other medicines. Call 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).

Serious birth defects

- **Tracleer can cause serious birth defects if taken during pregnancy. You must not be pregnant when you start taking Tracleer or during Tracleer treatment. Serious birth defects from Tracleer can happen early in pregnancy. Females who are able to get pregnant must have a negative pregnancy test before starting treatment and each month during Tracleer treatment.**
- Talk with your healthcare provider or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. Do not have unprotected sex. Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.
- Females who are able to get pregnant must use birth control (contraception) during Tracleer treatment. **You must choose and use two reliable forms of birth control at the same time, unless you have had a tubal sterilization, or have a Copper T 380A IUD or LNg 20 IUS inserted. These methods can be used alone.**
- **Birth control pills, shots, patches, and implants should not be used alone because they are not reliable when you are taking Tracleer. You must choose and use two reliable forms of birth control at the same time.**
- **If you have had a tubal sterilization, or have an IUD, these methods can be used alone. Otherwise, you should use two forms of birth control.**

Talk with your healthcare provider about which 2 methods of reliable birth control you should use. Your healthcare provider may recommend that you use a different method of birth control to help lower your risk of problems with your pulmonary arterial hypertension. See the end of this Medication Guide for more information about reliable methods of contraception during treatment with Tracleer.

See "What are the possible side effects of Tracleer?" for more information about side effects.

See the chart below for more information about reliable methods of contraception during treatment with Tracleer.

Reliable methods of contraception during treatment with Tracleer

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

REFERENCES

1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. February 2011.
2. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for arterial hypertension. *N Engl J Med.* 2002;896-903.
3. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin receptor bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001;358:1119-1123.

Service and support essentials

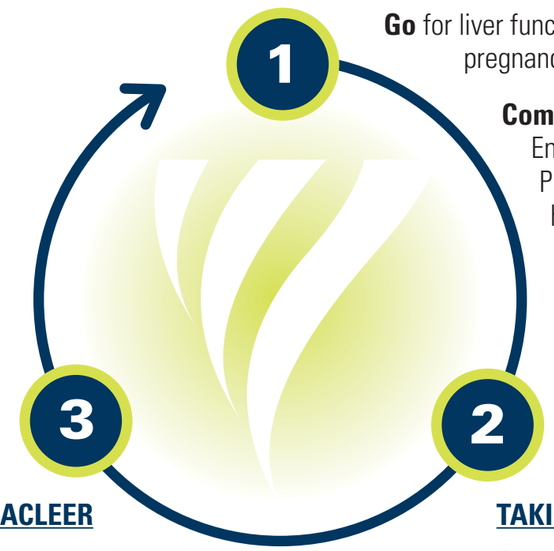
Tracleer Access Program (T.A.P.®)

Because of the risks of liver injury and birth defects associated with treatment, you must be enrolled in T.A.P. to receive Tracleer. This is done when you and your healthcare provider complete the Tracleer Enrollment for Patients and Prescribers form. T.A.P. is administered by PAH Pathways®. PAH Pathways counselors coordinate with your certified specialty pharmacy to make sure you receive your Tracleer. You can learn more about specialty pharmacies on page 7.

You can reach PAH Pathways, which administers T.A.P., by calling toll-free at 1-866-ACTELION (1-866-228-3546).

Please see accompanying full prescribing information, including ***BOXED WARNING*** *about liver damage and birth defects, and Medication Guide.*

Starting, taking, and renewing Tracleer



STARTING TRACLEER

Review the Medication Guide with your healthcare provider

Go for liver function and pregnancy tests

Complete the Tracleer Enrollment for Patients and Prescribers form with your healthcare provider

TAKING TRACLEER

Receive Tracleer from your specialty pharmacy

Go for monthly liver function and pregnancy tests

RENEWING TRACLEER

Your healthcare provider will complete the Tracleer Renewal form every year

Tracleer® BOSENTAN TABLETS

1 Starting Tracleer

Review the Medication Guide with your healthcare provider

The Medication Guide is in the back pocket. It covers important facts about Tracleer that you must understand before you start Tracleer, including the risks of liver injury and serious birth defects. Talk with your healthcare provider if you have any questions.

Go for your liver function and pregnancy tests

Before you start Tracleer, you must have a blood test to check your liver function. You must also have a pregnancy test before you start Tracleer, if you are able to become pregnant. You should not start Tracleer if you are pregnant.

Complete the Tracleer Enrollment for Patients and Prescribers form with your healthcare provider

Before you start Tracleer, you must consent to be enrolled in the Tracleer Access Program (T.A.P.®) and agree to comply with the requirements of the program as outlined on the back of the Tracleer Enrollment for Patients and Prescribers form.

Patient Agreement

- I have reviewed the Medication Guide with my healthcare provider. I understand that a Medication Guide will be provided to me each time I receive a prescription for Tracleer, and that I must read it each time because it may have new information important to my treatment.
- I authorize my healthcare providers, health plans, other payers, and pharmacies to disclose my personal, medical, and health information to Actelion Pharmaceuticals US, Inc., and its employees, distributors, agents, and contractors ("Actelion"), and I authorize Actelion to use and disclose this information for use in implementing T.A.P. including to: 1) establish my benefit eligibility; 2) communicate with my healthcare providers, health plans, other payers, and pharmacies about my medical care; 3) provide support services, including facilitating the provision of Tracleer to me; and 4) try to help find ways to pay for Tracleer, or for treatment or healthcare operations in progress.
- I have been informed of the risks of treatment with Tracleer, including the risks of liver damage and birth defects. I understand that I will be contacted by Actelion, its agents, and/or a healthcare provider to receive counseling on the risks of Tracleer treatment, to ensure that I am completing the required liver function tests and pregnancy tests (for females of childbearing potential—see definition below) and, if I am a female who becomes pregnant, to obtain information about my pregnancy.
- I agree to notify Actelion or my specialty pharmacy if I should change prescribers.
- I agree to have monthly blood tests as ordered by my healthcare provider for as long as I take Tracleer.
- I understand that Actelion cannot guarantee that it will be able to find ways to pay for my Tracleer, and I know that I am responsible for the costs of my care.
- I understand that I may be contacted by Actelion or its delegates regarding important safety surveys while I am taking Tracleer.
- I understand that once my health information has been disclosed to Actelion, privacy laws may no longer restrict its use or disclosure; however, Actelion agrees to protect my information by using and disclosing it only for the purposes described above or as required by law.
- I acknowledge and agree that, although Actelion will have access to my personal health information, Actelion will not be providing counseling or medical advice regarding my condition. I further understand that all questions regarding my medical and health conditions should be discussed with my healthcare provider.
- I consent to be in the Tracleer Access Program for as long as I am taking Tracleer.

Reference ID: 3334175
Page 25

2 Taking Tracleer

Receive Tracleer from your specialty pharmacy

Tracleer is not available in your retail pharmacy; rather, it is carried by a limited network of certified specialty pharmacies that deliver Tracleer directly to you.

To reduce the risks of the use of Tracleer, you must have liver function and pregnancy tests each month (see below). Your specialty pharmacy will call you to confirm that you have had your tests before they deliver your Tracleer. The specialty pharmacies are required to document that you have had your tests each month.

If you don't confirm with your specialty pharmacy that you have had your tests or if you become pregnant, your specialty pharmacy will not be able to ship Tracleer to you and will contact your healthcare provider. It's important that you do not stop taking Tracleer unless your doctor tells you to do so. Suddenly stopping your treatment may cause your symptoms to get worse.

With each monthly delivery, you will receive a Medication Guide, which you should read each time because there may be new information.

Go for monthly liver function and pregnancy tests

Each month, you must have a blood test to check your liver function. If you are able to become pregnant, you must also have a monthly pregnancy test. For more details about why these monthly tests are important and how to avoid becoming pregnant while taking Tracleer, please see the Medication Guide.

3 Renewing Tracleer

Renew Tracleer enrollment with your healthcare provider every year

Your healthcare provider will renew your enrollment in the Tracleer Access Program every year. Your healthcare provider will review the Medication Guide with you and complete the Tracleer Renewal form.

*Please see accompanying full prescribing information, including **BOXED WARNING** about liver damage and birth defects, and Medication Guide.*

Tracleer® BOSENTAN TABLETS

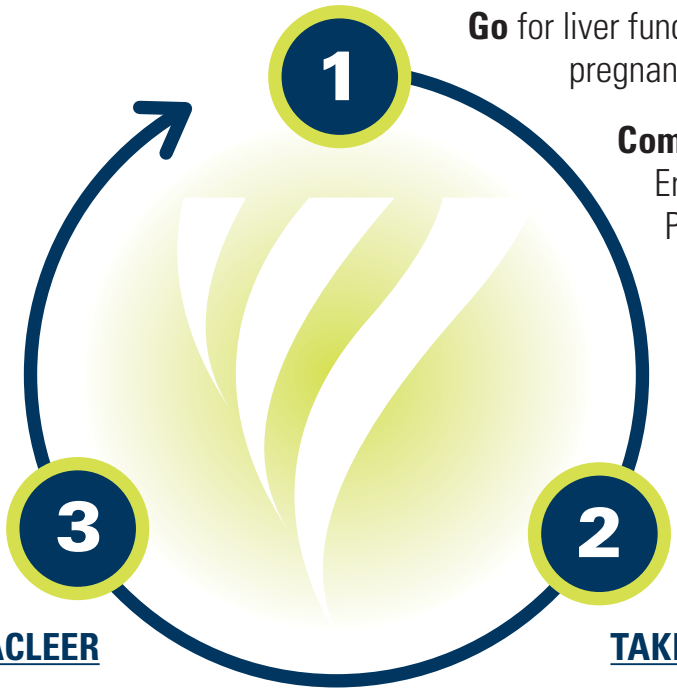
Starting, taking, and renewing Tracleer

STARTING TRACLEER

Review the Medication Guide with your healthcare provider

Go for liver function and pregnancy tests

Complete the Tracleer Enrollment for Patients and Prescribers form with your healthcare provider



TAKING TRACLEER

Receive Tracleer from your specialty pharmacy

Go for monthly liver function and pregnancy tests

RENEWING TRACLEER

Your healthcare provider will complete the Tracleer Renewal form every year

If you have questions about Tracleer enrollment and renewal, or if you would like more information about Tracleer, you can reach PAH Pathways, which administers T.A.P., by calling toll-free at 1-866-ACTELION (1-866-228-3546).

*Please see accompanying full prescribing information, including **BOXED WARNING** about liver damage and birth defects, and Medication Guide.*

PAHPathways®
ACTELION SERVICES & SUPPORT

Tracleer Access Program (.

Tracleer®
BOSENTAN TABLETS

ACTELION

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www.TRACLEER.com

Important reminders for patients taking Tracleer® (bosentan)

PAHPathways™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

You can reach PAH Pathways, which administers T.A.P., by calling toll-free at 1-866-ACTELION (1-866-228-3546) or visiting pahpathways.com or tracleer.com

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Monthly liver tests

You must have a blood test to check your liver function before you start Tracleer and each month after that.

- Call your healthcare provider right away if you have any of these symptoms of liver problems: nausea, vomiting, fever, unusual tiredness, abdominal (stomach area) pain, or yellowing of the skin or the whites of your eyes (jaundice).

Monthly pregnancy tests

You must not be pregnant when you start taking Tracleer or during Tracleer treatment. **Females who are able to get pregnant must have a negative pregnancy test before starting treatment and each month during Tracleer treatment.** Talk with your healthcare provider to find out about how to prevent pregnancy.

- Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.

Tracleer® (bosentan) Renewal

Please complete and fax this form to PAH Pathways® at 1-866-279-0669. The information will be entered into the Tracleer Access Program (T.A.P.®) database. You can also reach PAH Pathways via phone at 1-866-ACTELION (1-866-228-3546) or by mail at PO Box 826, South San Francisco, CA 94083-0826.

Patient Information			
First name:	MI:	Last name:	
Gender: ☐ Male ☐ Female	SSN:	DOB:	
Primary language:			
E-mail address:			
Phone #:	Alternate phone #:		
Best time to call:			
Address:			
City:	State:	ZIP:	
Legal guardian/emergency contact:			
Relationship:	Phone #:		

Prescriber and Prescription Information			
First name:	MI:	Last name:	
E-mail address:		Degree:	
DEA #:	NPI #:	Tax ID #:	State license #:

Complete section below only if your contact information has changed

Facility name:		Affiliated hospital:		
Specialty:		Office contact (name and phone):		
Office e-mail address:	Phone #:			Fax #:
Primary address:	City:	State:	ZIP:	Preferred method of contact: ☐ Phone ☐ Fax ☐ E-mail

For renewal patients, please indicate whether:

1. You have reviewed liver function tests. ☐ Yes ☐ No

2. If a female, she is of childbearing potential. ☐ Yes ☐ No

3. If a female of childbearing potential, you have confirmed a negative pregnancy test. ☐ Yes ☐ No

By signing, I certify that I have counseled my patient on the risks of Tracleer and renewed their enrollment in the Tracleer Access Program.

Prescriber signature: _____ Date: _____

Definition of Female of Childbearing Potential (FCBP)

Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).

Reliable methods of contraception during treatment with Tracleer

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Vaginal ring —Transdermal patch • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

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Tracleer® (bosentan) Prescriber Certification

Please complete and fax this form to PAH Pathways® at 1-866-279-0669. The information will be entered into the Tracleer Access Program (T.A.P.®) database. You can also reach PAH Pathways via phone at 1-866-ACTELION (1-866-228-3546) or by mail at PO Box 826, South San Francisco, CA 94083-0826.

Prescriber Information

First name:	MI:	Last name:
Degree:	E-mail address:	
DEA #:	NPI #:	
Tax ID #:	State license #:	

Complete section below only if you are a new prescriber or your contact information has changed.

Name of facility:		Affiliated hospital:		
Specialty:		Office contact (name and phone):		
Office e-mail address:		Phone #:		Fax #:
Primary address:	City:	State:	ZIP:	Preferred method of contact: ☐ Phone ☐ Fax ☐ E-mail

Prescriber Certification—My signature below certifies that:

1. I have read and understood the communication and educational materials for prescribers regarding the risks of Tracleer, and agree to document that I:
   - Reviewed and discussed the Medication Guide and the risks of Tracleer (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   - Reviewed liver function tests (ALT/AST/bilirubin) and confirmed that my patients are not pregnant (if applicable), and I agree to order and monitor monthly liver function tests and, if applicable, pregnancy tests.
   - Educated and counseled females of childbearing potential to notify me if they suspect they may be pregnant.
   - Educated and counseled females of childbearing potential about the need to use reliable methods of contraception during treatment with Tracleer and for one month after treatment discontinuation.
2. I will notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer.
3. I will counsel my patients who fail to comply with the program requirements.
4. I will renew my patients' T.A.P. enrollment annually by completing and submitting a new form for patients continuing therapy.

Prescriber signature: _____ Date: _____

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Tracleer Access Program Hospital Certification

Please complete and fax this form to PAH Pathways® at 1-866-279-0669. The information will be entered into the Tracleer Access Program (T.A.P.®) database. You can also reach PAH Pathways via phone at 1-866-ACTELION (1-866-228-3546) or by mail at PO Box 826, South San Francisco, CA 94083-0826.

Because of the risks of hepatotoxicity and teratogenicity, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.), which is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). In order to receive Tracleer, prescribers, patients, pharmacies, and hospitals must enroll in T.A.P. and agree to comply with the requirements of the program.

This hospital acknowledges that:

1. This hospital will establish systems, order sets, protocols, or other measures to limit the use of Tracleer as outlined below and to ensure appropriate liver function and pregnancy tests are performed.
2. Tracleer will be dispensed only to inpatients who are under the supervision and care of a healthcare provider who has been certified in the Tracleer Access Program.
3. Tracleer will be dispensed only to inpatients who are enrolled in the Tracleer Access Program or who will be enrolled prior to discharge from this hospital.
4. This hospital will dispense no more than a seven- (7-) day supply of Tracleer in a child-resistant container upon discharge of the patient.
5. A Tracleer Medication Guide will be provided to the patient prior to discharge from this hospital (available for download at www.TRACLEERREMS.com).
6. This hospital agrees to report adverse reactions to Actelion Pharmaceuticals US, Inc. (Actelion), including hepatotoxicity, and to report any pregnancy during treatment with Tracleer.
7. This hospital agrees to re-certify every three (3) years.
8. This hospital agrees to develop a system to track its compliance with the conditions above and provide information about its compliance to Actelion and/or the Food and Drug Administration upon request.

Signature: _____

Facility name:		Authorized designee name:
Authorized designee title:	☐ Hospital pharmacist ☐ Head of P & T committee ☐ Other title : _____	
Facility identification: (Please complete one of the following)	☐ Health industry number (HIN#) _____ ☐ National provider identifier (NPI#) _____ ☐ DEA# _____ ☐ Other identifier : _____	
Facility address:		
City:	State:	ZIP:
Facility phone:	Fax:	
Authorized designee phone:	Fax:	
Authorized designee e-mail:		

I confirm that the above information is correct.

I understand that the information on this form will be used by Actelion and/or its agents to identify hospitals that have been certified in the Tracleer Access Program. I further understand that Actelion will share this information with certified wholesale specialty pharmacies for the purpose of allowing my hospital to purchase Tracleer, and may share this information with individuals or entities assisting Actelion with compliance with the Tracleer REMS Program. At any time, this information may be shared with government agencies for the purposes of assessing the Tracleer Access Program.

I further understand that Actelion will regularly monitor program compliance to ensure that program objectives are being met. Actelion reserves the right to terminate a hospital's certification at any time based on the hospital's noncompliance with program requirements or take other appropriate measures to assure that the program objectives are met.

Date: _____

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PAHPathways®
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

[Month XX, 2012]

IMPORTANT PRESCRIBING INFORMATION

Subjects:

- **Changes to the Tracleer Access Program (T.A.P.®): Required Hospital Certification**
- **Availability of Tracleer® (bosentan) 30-Unit Blister Packs, for Hospital Use Only**

Dear Hospital,

Actelion Pharmaceuticals US, Inc. (Actelion), would like to inform you of important changes in the requirements for dispensing Tracleer in the inpatient setting, and the introduction of blister pack dosing units for hospital use.

Because of the risks of hepatotoxicity and teratogenicity, Tracleer has a **BOXED WARNING** and is available only through a restricted program called the Tracleer Access Program (T.A.P.), which is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, pharmacies, and hospitals must enroll in the program. For more information about T.A.P. and the requirements of the program, please see **www.TracleerREMS.com** or call 1-866-ACTELION (1-866-228-3546).

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO class II patients, which may preclude future use as their disease progresses.

Impact on Hospitals:

In the inpatient setting, Tracleer is available only to certified hospitals. Hospitals will be required to complete a Tracleer Access Program Hospital Certification form (enclosed). Only certified wholesale specialty pharmacies will distribute to certified hospitals. As part of the certification, the certified hospital will be required to dispense no more than a 7-day supply in child-resistant packaging to any enrolled patient, along with a Medication Guide, upon discharge. New patients must be enrolled in T.A.P. upon discharge.

Process for Hospital Certification

- An authorized designee from the hospital must complete the Tracleer Access Program Hospital Certification form and provide it to PAH Pathways®.
- PAH Pathways will contact the hospital to confirm receipt of the Tracleer Access Program Hospital Certification form and will enter the hospital information into the T.A.P. database.
- PAH Pathways will provide the hospital with the contact information of the certified wholesale specialty pharmacy.
- PAH Pathways will provide a regularly updated list of all certified hospitals from the database to certified wholesale specialty pharmacies. Pharmacies will only process requests to distribute Tracleer to certified hospitals.
- Hospitals must recertify every 3 years.

Hospitals can contact T.A.P. to confirm patient and prescriber enrollment in T.A.P. by calling 1-866-228-3546.

Blister Packs for Hospital Use Only

The "How Supplied" section of the Tracleer full prescribing information has been revised to include the addition of 30-unit blister packs for hospital use only.

Important Safety Information

Tracleer can be prescribed and dispensed only through a restricted distribution program (Tracleer Access Program) because of the risks of hepatotoxicity and teratogenicity.

Hepatotoxicity. Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Teratogenicity. Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNg-20 IUS inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests. Hormonal contraceptives may not be reliable when Tracleer is co-administered.

Please see accompanying full prescribing information, including **BOXED WARNING** about hepatotoxicity and teratogenicity.

Contraindications

Tracleer is contraindicated with cyclosporine A, with glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

Adverse Event Reporting

To report suspected adverse reactions, contact Actelion at 1-866-ACTELION (1-866-228-3546), or FDA at 1-800-FDA-1088 or **www.fda.gov/medwatch**.

A copy of the revised full prescribing information and Medication Guide for Tracleer are enclosed for your reference. If you have any questions, please contact your local Tracleer representative or Actelion at the number above.

Sincerely,

[Signature]

Senior Vice President, US Medical
Actelion Pharmaceuticals US, Inc.

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PAHPathways®
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

[Month XX, 2012]

IMPORTANT PRESCRIBING INFORMATION

Subjects:

- **Changes to the Tracleer Access Program (T.A.P.®)**
- **Availability of Tracleer® (bosentan) 30-Unit Blister Packs, for Hospital Use Only**

Dear Tracleer Prescriber,

Actelion Pharmaceuticals US, Inc. (Actelion), would like to inform you of important changes in the requirements for dispensing Tracleer in the inpatient setting, and the introduction of blister pack dosing units for hospital use.

Because of the risks of hepatotoxicity and teratogenicity, Tracleer has a **BOXED WARNING** and is available only through a restricted program called the Tracleer Access Program (T.A.P.), which is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, pharmacies, and hospitals must enroll in the program. For more information about T.A.P. and the requirements of the program, please see **www.TracleerREMS.com** or call 1-866-ACTELION (1-866-228-3546).

PROGRAM CHANGES

Impact on Tracleer Prescribers

As a certified Tracleer prescriber, you will continue to be required to educate your patients about the risks of Tracleer, the importance of monthly liver function and pregnancy testing, and the need for females of childbearing potential to use reliable methods of contraception and not to become pregnant. You also must continue to monitor your patients' liver function and pregnancy test results monthly, and counsel your patients as needed.

Initiating Tracleer in a Certified Hospital

Hospitals must be certified before initiating use of Tracleer in an inpatient setting.

- Tracleer may be dispensed only to inpatients who are under the supervision and care of a healthcare provider who has been certified in T.A.P.
  - Complete the Tracleer Prescriber Certification form confirming you are aware of and have fulfilled essential steps that will help ensure the ongoing safe use of Tracleer.
  - Send the completed Tracleer Prescriber Certification form to PAH Pathways®, the administrator of T.A.P., by fax at 1-866-279-0669. The information will be entered in the T.A.P. database.
- Ensure your patient has been enrolled in the Tracleer Access Program prior to discharge from the hospital.
  - Complete the Tracleer Enrollment for Patients and Prescribers form with your patient and send it to PAH Pathways by fax at 1-866-279-0669.
  - PAH Pathways will then work with a certified specialty pharmacy to ensure your patient receives Tracleer in the outpatient setting.
- Ensure baseline liver monitoring has been conducted and pregnancy has been excluded in females of childbearing potential.

Follow usual procedures related to the distribution of medicines within your specific hospital or inpatient pharmacy setting. No more than a 7- (seven-) day supply of Tracleer in childproof packaging may be provided to the patient upon discharge.

Other Changes to the Tracleer Access Program (T.A.P.)

The Tracleer Access Program has further been updated to include the following:

- A new website, **www.TracleerREMS.com**, provides information about the Tracleer Access Program.
- Updates to the Tracleer Enrollment for Patients and Prescribers form.
- A new stand-alone Prescriber Certification form. Prescribers may now certify either by completing the Tracleer Enrollment for Patients and Prescribers form or by completing the new Prescriber Certification form.
- A new stand-alone Tracleer Renewal form. Annual patient re-enrollment may now be done by certified prescribers only (without requiring patient consent), by completing the Tracleer Renewal form.

What Has Not Changed with the Tracleer Access Program

- Because of the risks of hepatotoxicity and teratogenicity, Tracleer continues to be available only through a restricted distribution program (T.A.P.).

- All patients on Tracleer must be enrolled in T.A.P. and their enrollment must be renewed annually by their certified prescriber.
- All prescribers must be specially certified in T.A.P. in order to prescribe Tracleer in any setting.
- Only specialty pharmacies who have been specially certified in T.A.P. may dispense Tracleer in the outpatient setting.

For more information regarding hospital certification, please see **www.TracleerREMS.com**, or contact PAH Pathways at 1-866-ACTELION (1-866-228-3546) for documentation and certification information.

Indication

Tracleer® (bosentan) is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO class II patients, which may preclude future use as their disease progresses.

Important Safety Information

Tracleer can be prescribed and dispensed only through a restricted distribution program (Tracleer Access Program) because of the risks of hepatotoxicity and teratogenicity.

Hepatotoxicity. Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Teratogenicity. Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNg-20 IUS inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests. Hormonal contraceptives may not be reliable when Tracleer is co-administered.

Please see accompanying full prescribing information, including **BOXED WARNING** about hepatotoxicity and teratogenicity.

Contraindications

Tracleer is contraindicated with cyclosporine A, with glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

Adverse Event Reporting

To report suspected adverse reactions, contact Actelion at 1-866-ACTELION (1-866-228-3546), or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

A copy of the revised full prescribing information and Medication Guide for Tracleer are enclosed for your reference. If you have any questions, please contact your local Tracleer representative or Actelion at the number above.

Sincerely,

[Signature]

Senior Vice President, US Medical
Actelion Pharmaceuticals US, Inc.

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Tracleer BOSENTAN TABLETS

TRACLEER REMS

The Risk Evaluation and Mitigation Strategy (REMS) Program for Tracleer

About the Tracleer REMS Program

The Tracleer REMS Program is the Risk Evaluation and Mitigation Strategy (REMS) for Tracleer® (bosentan).

A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risk(s) associated with a drug product, and is required by the Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. In order for Actelion to communicate certain risks about Tracleer, Actelion has worked with the FDA to develop materials to communicate the risks of:

- Hepatotoxicity
- Birth defects

Because of these risks, Tracleer is only available through a restricted distribution program. The goals of the Tracleer REMS Program are to:

- Enable informed risk-benefit decisions for treating patients with Tracleer.
- Minimize the risk of hepatotoxicity in patients who are exposed to Tracleer.
- Minimize the risk of fetal exposures in female patients who are exposed to Tracleer.
- Educate prescribers, patients, and pharmacies on the safe-use conditions for Tracleer.

The Tracleer REMS program is designed to inform patients and prescribers about the risks associated with Tracleer. To learn more about the serious risks please see full Prescribing Information, including **BOXED WARNING** about hepatotoxicity and teratogenicity.

Tracleer Access Program (T.A.P.®)

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.). T.A.P. is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, hospitals, and pharmacies must enroll in the program. Enrollment in T.A.P. is accomplished by completing and submitting the Tracleer Enrollment for Patients and Prescribers form. T.A.P. is administered by PAH Pathways®. You can reach PAH Pathways by calling toll-free at 1-866-ACTELION (1-866-228-3546).

Certified specialty pharmacies

Tracleer is not dispensed through retail pharmacies; rather, Tracleer is dispensed through a restricted network of certified specialty pharmacies. Specialty pharmacies help with patient management by confirming required monthly liver function and pregnancy testing. Specialty pharmacies also arrange for Tracleer to be delivered conveniently and directly to patients each month. If a patient does not confirm having the monthly tests or becomes pregnant, the pharmacy will contact you.

Essential Roles and Responsibilities for Prescribers

1. Plan to prescribe Tracleer

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

You must address and document (see step 2) [illegible] every Tracleer enrollment:

these points with every Tracleer enrollment.

- Before prescribing Tracleer, review the Medication Guide and discuss the risks of treatment with your patients, including the risks of hepatotoxicity and teratogenicity.
- Order and review liver function tests (ALT/AST/bilirubin) and confirm that your female patients of childbearing potential are not pregnant.
  - Female patients who are physically capable of becoming pregnant include those who are pubertal and have not yet had menses (premenarchal, Tanner stage 3, 11.5 to 13 years of age), perimenopausal and have had spontaneous menses in the last 24 months, and nonmenopausal who have not had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.
  - Female patients who are not considered to be of childbearing potential are surgically sterile (both ovaries and/or uterus removed), postmenopausal (no menstrual period for longer than 24 consecutive months, confirmed by their healthcare provider), or incapable of pregnancy (confirmed by their healthcare provider).
- Agree to order and monitor monthly liver function and, if applicable, pregnancy tests.
- Educate and counsel females of childbearing potential on the need to use reliable methods of contraception during treatment with Tracleer and for 1 month after treatment discontinuation. See the table "Reliable methods of contraception" below.

Reliable methods of contraception during treatment with Tracleer[1]

Methods to use alone	Hormone (choose 1 and use with a barrier method)	Barrier (use both OR choose 1 and use with a hormone method)
• Intrauterine devices (IUDs) —Copper T 380A IUD —LNg-20 IUS (progesterone IUD) • Tubal sterilization	• Estrogen and progesterone —Oral contraceptives —Transdermal patch —Vaginal ring • Progesterone only —Injection —Implant	• Male condom with spermicide • Diaphragm with spermicide OR Cervical cap with spermicide
	A partner's vasectomy still requires 1 additional method of contraception.	

- Educate and counsel females of childbearing potential to notify you if they suspect they may be pregnant.
  You must also agree to:
- Counsel any patient who fails to comply with the program requirements
- Notify Actelion Pharmaceuticals US, Inc., and/or the FDA, of any adverse events, including hepatotoxicity, and report any pregnancy during treatment with Tracleer
- Renew your patients' Tracleer enrollment annually by completing and submitting the Tracleer Renewal form

The Patient Essentials Guide is available to help you discuss the steps of Tracleer enrollment and renewal with your patients. The Tracleer Medication Guide, which you must review with your patients prior to prescribing Tracleer, is included in its entirety in the back pocket of the Patient Essentials guide.

2. Submit Tracleer Enrollment for Patients and Prescribers form

To enroll your patients in T.A.P.® with each Tracleer Enrollment for Patients and Prescribers form you must:

- Read and complete it in its entirety
- Sign the Prescriber Certification (only if you are not currently a certified prescriber).
- Complete and sign the prescription information
- Document patient consent to the terms of the Tracleer Enrollment for Patients and Prescribers form
- Fax the form to 1-866-279-0669

Keep copies of all completed Tracleer Enrollment for Patients and Prescribers forms.

3. Monitor liver function and pregnancy test results monthly

The use of Tracleer requires that you obtain and review monthly liver function and, if applicable, pregnancy tests. You must counsel your patients about the importance of monthly testing and ensure that test results are obtained and reviewed by your office. The specialty pharmacy will confirm with your patients that monthly tests have been obtained. If a patient does not confirm having the monthly tests or becomes pregnant, the pharmacy will contact you. Notify Actelion and/or the FDA of any pregnancies or adverse events, including liver injury, by calling toll-free at 1-866-ACTELION (1-866-228-3546).

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

Tracleer aminotransferase (ALT/AST) management[1]

ALT/AST[1]	Treatment and monitoring recommendations

[illegible]	[illegible]
≤3 x ULN*	**Continue to monitor; no change in monitoring schedule or dosage**
>3 to ≤5 x ULN	**Confirm** by another test; **if confirmed, reduce the dose or interrupt** treatment and monitor LFT levels every 2 weeks **Continue or reintroduce**† **Tracleer** if levels return to pretreatment levels
>5 to ≤8 x ULN	**Confirm** by another test; if confirmed, stop therapy; monitor LFTs at least every 2 weeks **Continue** reintroduction† of therapy if LFTs return to pretreatment levels
>8 x ULN	**Stop** therapy; do not reintroduce

** 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.

4. Renew Tracleer enrollment annually

Annually, you must renew your patient in the Tracleer Access Program (T.A.P.®). By renewing your patients in T.A.P., you are agreeing that you have counseled them on the risks and benefits of Tracleer. You may renew your patient by completing the Tracleer Renewal form.

Enrollment Forms and Resources

T.A.P. Prescribing Materials	T.A.P. Hospital Certification	T.A.P. Patient Materials
• Tracleer Full Prescribing Information • Tracleer Enrollment for Patients and Prescribers form • Tracleer Renewal form • Prescriber Certification form • Prescriber Essentials Guide • Dear Prescriber Letter • Patient Essentials Guide	• T.A.P. Hospital Certification form • Dear Hospital Letter	• Tracleer Medication Guide • Patient Essentials Guide

Hospital Certification

In the inpatient setting, Tracleer is only available to certified hospitals. To become certified a hospital must complete the T.A.P. Hospital Certification form, acknowledging that:

1. The hospital will establish systems, order sets, protocols, or other measures to limit the use of Tracleer as outlined below and to ensure appropriate liver function and pregnancy tests are performed.
2. Tracleer will be dispensed only to inpatients who are under the supervision and care of a healthcare provider who has been certified in the Tracleer Access Program.
3. Tracleer will be dispensed only to inpatients who are enrolled in the Tracleer Access Program or who will be enrolled prior to discharge from this hospital.
4. The hospital will dispense no more than a seven- (7-) day supply of Tracleer in a child-resistant container upon discharge of the patient.
5. A Tracleer Medication Guide will be provided to the patient prior to discharge from this hospital.
6. The hospital agrees to report adverse reactions to Actelion Pharmaceuticals US, Inc. (Actelion), including hepatotoxicity, and to report any pregnancy during treatment with Tracleer.
7. The hospital agrees to re-certify every three (3) years.
8. The hospital agrees to develop a system to track its compliance with the conditions above and provide information about its compliance to Actelion and/or the Food and Drug Administration upon request.

For more information on the program, please contact PAH Pathways, who administers T.A.P., at 1-866-228-3546.

Hospital Certification Process

- An authorized designee from the hospital must complete the T.A.P. Hospital Certification form and provide it to PAH Pathways.
- PAH Pathways will contact the hospital to confirm receipt of the T.A.P. Hospital Certification form and will enter the hospital information into T.A.P.
- PAH Pathways will provide the hospital with the contact information of the certified wholesale specialty pharmacy.
- PAH Pathways will provide a regular updated list of all certified hospitals from the database to certified wholesale specialty pharmacies. Pharmacies will only process requests to distribute Tracleer to certified hospitals.

- Hospitals must re-certify every 3 years.

Hospitals can contact T.A.P. to confirm patient and prescriber enrollment into T.A.P. by calling 1-866-228-3546.

Ordering Information

Tracleer is only available for distribution by specialty pharmacies who have been certified in T.A.P. A select number of T.A.P. certified specialty pharmacies will also have the ability to wholesale Tracleer to hospitals. Once a hospital has been enrolled in T.A.P., PAH Pathways will confirm enrollment with the hospital and provide futher instructions for how to purchase Tracleer via one of the select certified specialty pharmacies.

INDICATION

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

Considerations for use

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

IMPORTANT SAFETY INFORMATION

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer Access Program (T.A.P.), which is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program, by calling T.A.P at 1-866-228-3546.

Hepatotoxicity

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (>3 x ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 x ULN.

Teratogenicity

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNg-20 IUS inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests.

CONTRAINDICATIONS

Tracleer is contraindicated with cyclosporine A, with glyburide, in females who are or may become pregnant, or in patients who are hypersensitive to bosentan or any component of Tracleer.

WARNINGS AND PRECAUTIONS

In clinical trials, ALT/AST elevations (>3 x ULN) were observed in 11% of patients treated with Tracleer, accompanied by elevated bilirubin in a few cases. The combination of hepatocellular injury (increases in aminotransferases of >3 x ULN) and increases in total bilirubin (≥2 x ULN) is a marker for potential serious hepatotoxicity. Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Avoid using Tracleer in patients with moderate or severe liver impairment or elevated ALT/AST >3 x ULN prior to drug initiation.

If clinically significant fluid retention develops, with or without associated weight gain, the cause, such as Tracleer or underlying heart failure, must be determined. Patients may require treatment or Tracleer therapy may need to be discontinued.

If signs of pulmonary edema occur, consider the diagnosis of associated pulmonary veno-occlusive disease and consider discontinuing Tracleer.

Decreased sperm counts have been observed in patients receiving Tracleer. Preclinical data also suggest that Tracleer, like other endothelin receptor antagonists, may have an adverse effect on spermatogenesis.

Treatment with Tracleer can cause a dose-related decrease in hemoglobin (Hgb) and hematocrit. Hgb should be checked after 1 and 3 months, and then every 3 months. Upon marked decrease in Hgb, determine the cause and need for specific treatment.

ADVERSE EVENTS

In Tracleer pivotal trials, the most common adverse events occurring more often in Tracleer-treated patients than in patients taking placebo were respiratory tract infection (22% vs 17%), headache (15% vs 14%), edema (11% vs 9%), chest pain (5% vs 5%), syncope (5% vs 4%), flushing (4% vs 3%), hypotension (4% vs 2%), sinusitis (4% vs 2%), arthralgia (4% vs 2%), serum aminotransferases abnormal (4% vs 2%), palpitations (4% vs 2%), and anemia (3% vs 0%).

Please see full Prescribing Information, including **BOXED WARNING** about hepatotoxicity and pregnancy.

References

1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. October 2012.

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TRA-00088

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/s/

MARY R SOUTHWORTH
07/01/2013