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

January 31, 2010

Document No: D-10.076

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, and pharmacies on the safe-use conditions for Tracleer.

II. REMS ELEMENTS

A. Medication Guide

A Medication Guide will be dispensed with each 30-day supply of Tracleer 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 and Renewal Form each time he or she prescribes Tracleer, 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 a validated (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

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

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

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

i. Tracleer Enrollment and Renewal Form

ii. Prescriber Essentials guide

iii. Prescriber letter

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

a. Actelion will ensure that Tracleer dispensers are specially certified. Tracleer will only be dispensed by pharmacies that are specially certified. Actelion will ensure that, to be certified, they are under legal contract and that they 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 liver injury and serious birth defects

2. on the need to complete a monthly liver function test and pregnancy test (for FCBP as defined on the Tracleer Enrollment and Renewal Form)

iii. Counsel all FCBP on the need to use reliable contraception (as defined in the Tracleer Enrollment and Renewal Form) 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 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. validated database

xii. Notify Actelion of any reports of adverse events, including liver injury, 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.

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

i. is trained on the REMS program.

ii. trains pharmacy staff on the REMS program procedures and REMS materials prior to dispensing Tracleer

iii. agrees that the certified pharmacy may be audited by the FDA, Actelion, or a third party designated by Actelion

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

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

ii. Prescriber letter from certified pharmacy (accompanies FRM-549-COP-US)

iii. Patient Information Sheet (to be provided to the patient by the certified pharmacy)

3. Tracleer will only be dispensed to patients 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. 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.

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

i. Patient Essentials Guide

C. Implementation System

The Implementation System includes the following:

1. Actelion will maintain a database capturing certified prescribers, pharmacies and patients. Actelion will create a new reporting database that will link adverse events

of interest extracted from the Drug Safety database (Argus Safety™) with relevant information, such as enrolled patients, certified prescribers and pharmacies.

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. Therefore, the distribution data will be the same as the prescription data.

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

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 and Renewal

Check one: ☐ **Enrollment** ☐ **Renewal**

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

Once complete, submit this form to PAH Pathways.™ The information will be entered into the Tracleer Access Program (T.A.P.®) database and forwarded to the specialty pharmacy you designate below. The specialty pharmacy will follow up as needed with prescribers and patients.

Patient Information

First name:	MI:	Last name:	Gender: ☐ Male ☐ Female
SSN:		DOB:	Phone #:
Address:		City:	State: ZIP:
Legal guardian/emergency contact:		Relationship:	Phone #:
Shipping directions: ☐ Physician office ☐ Patient's home ☐ Hospital		Shipping attn:	
Shipping address:		City:	State: ZIP:

Diagnosis: Pulmonary arterial hypertension (check subtypes): ☐ Familial ☐ Idiopathic ☐ Scleroderma ☐ HIV ☐ Lupus ☐ Portal hypertension ☐ Congenital heart defects ☐ Pulmonary hypertension—other etiologies: _____
☐ Other: _____

Required: Please submit copies of patient's current medical and prescription cards with this form.

Insurance Information

Primary insurance company:			Phone #:
Name of insured:		Policy #:	Group/Policy #:
Prescription coverage name:	Phone #:	Policy #:	Group/Policy #:

Indicate specialty pharmacy preference: _____

For a current list of pharmacies, call 1-866-228-3546. If no preference is indicated, 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:	Degree:
DEA #:		NPI:	

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

Name of facility:	Specialty:	Tax ID #:	State license #:
Office contact (name and phone):		Phone #:	Fax #:

Primary address:	City:	State:	ZIP:	E-mail:

For the patient indicated on this form, please indicate whether:

1. You have reviewed pretreatment 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 pretreatment negative pregnancy test. ☐ Yes ☐ No

☐ Tracleer 62.5 mg (66215-0101-06) Refills #: _____

☐ Tracleer 125 mg (66215-0102-06) Refills #: _____ Dispense as Written

Directions for use:

Prescriber signature: _____ Date: _____

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 bosentan (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   - –Reviewed pretreatment 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' prescriptions annually by completing and submitting a new form for patients continuing therapy.

Prescriber signature: _____ Date: _____

BEFORE SIGNING, SEE IMPORTANT SAFETY INFORMATION ON BACK.

Tracleer® (bosentan) Enrollment and Renewal

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 injury 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 I may be contacted by Actelion or its delegates regarding important safety surveys while I am taking Tracleer.
- I understand that Actelion does not promise to find ways to pay for my Tracleer, and I know that I am responsible for the costs of my care.
- 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.

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.

PAHPathways™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

Tracleer®
BOSENTAN TABLETS

Introduction to the essentials

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. 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 potential benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses. Prescribers of Tracleer must be aware of risks associated with treatment, including the risks of hepatotoxicity and teratogenicity.

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. To receive Tracleer, patients must be enrolled in the Tracleer Access Program (T.A.P.®), which is done by completing and submitting the Tracleer Enrollment and Renewal form. With each prescription (both initial enrollments and annual renewals), 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 is part of the Tracleer Enrollment and Renewal 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.

Service and support essentials

Tracleer Access Program (T.A.P.)

Because of the risks associated with treatment, the use of Tracleer requires participation in the Tracleer Access Program (T.A.P.), a restricted distribution program. In order to receive Tracleer, prescribers and patients must enroll in T.A.P. and agree to comply with the requirements of this program. Enrollment in T.A.P. is accomplished by completing and submitting the Tracleer Enrollment and Renewal 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.

Please see accompanying full prescribing information.

4 ESSENTIAL steps to enrollment and renewal

1 Plan to prescribe Tracleer

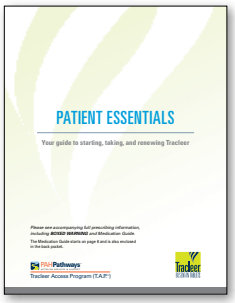
Tracleer is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these potential 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) these points with every Tracleer enrollment or renewal:

- 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 pretreatment 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 a new Tracleer Enrollment and 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 Patient Essentials guide and also in its back pocket.

Please see accompanying full prescribing information.

For patients with pulmonary arterial hypertension (PAH) WHO Class II-IV

2 Submit Tracleer Enrollment and Renewal form

Tracleer® (bosentan) Enrollment and Renewal

Check one: ☐ **Enrollment** ☐ **Renewal**

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

Once complete, submit this form to PAH Pathways.™ The information will be entered into the Tracleer Access Program® (TAP®) database and forwarded to the specialty pharmacy you designate below. The specialty pharmacy will follow up as needed with prescribers and patients.

ing directions: ☐ Physician office ☐ Patient's home ☐ Hospital

ing address:

osis: Pulmonary arterial hypertension (check subtypes): ☐ Familial ☐ Idiopathic ☐ Scleroderma ☐ HIV ☐ Lupus ☐ Portal hypertension ☐ Congenital heart defects ☐ Pulmonary hypertension—other etiologies: _____

☐ Other: _____

Please submit copies of patient's current medical and prescription cards with this form.

ry insurance company:

e of insured:

ription coverage name:

te specialty pharmacy preference:

current list of pharmacies, call 1-866-228-3546. If no preference is indicated, this referral will be sent to the appropriate specialty pharmacy based on the patient's existing benefits.

d 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 er Access Program, and I agree to comply with the program for as long as I am prescribed Tracleer.

uardian signature: _____

ame:

#:

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

e of facility:

contact (name and phone):

ry address:

r the patient indicated on this form, please indicate whether:

ou have reviewed pretreatment liver function tests. ☐ Yes ☐ No

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

f a female of childbearing potential, you have confirmed a pretreatment egative pregnancy test. ☐ Yes ☐ No

Tracleer 62.5 mg (66215-0101-06) Refills #: _____

Tracleer 125 mg (66215-0102-06) Refills #: _____ Dispense as Written

ections for use:

scriber signature: _____

GNING, SEE IMPORTANT SAFETY INFORMATION ON BACK.

Sign and Resend Confirmation

Keep copies of all completed Tracleer Enrollment and Renewal forms.

Fax the form to 1-866-279-0669

Document patient consent to the terms of the Tracleer Enrollment and Renewal form

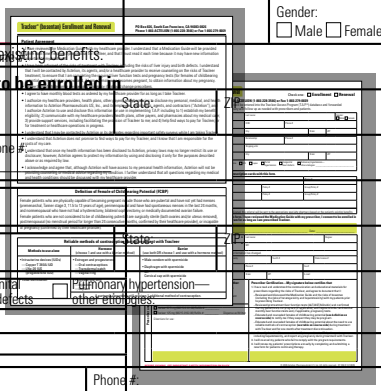
Complete and sign the prescription information

Read and complete it in its entirety

On the back of this form, have Quietil the Medication Guide with my prescriber, I consent to be enrolled in

you must:

ment and Renewal form



Patient Information

First name: | MI: | Last name: | Gender: ☐ Male ☐ Female

Address: | City: | State: | ZIP:

Legal guardian/emergency contact: | Relationship: | Phone #:

Shipping directions: ☐ Pick-Up-Rite ☐ Local courier ☐ Hospital | Shipping attn: | Degree:

Shipping address: | City: | State: | ZIP:

Diagnosis: Pulmonary arterial hypertension (check subtypes): ☐ Familial ☐ Idiopathic ☐ Scleroderma ☐ HIV ☐ Lupus ☐ Portal hypertension ☐ Congenital heart defects ☐ Pulmonary hypertension—other etiologies:

☐ Other: | Specialty: | Tax ID #: | State license #:

Required: Please submit copies of patient's current medical and prescription cards with this form.

Insurance Information

Primary insurance company: | Phone #: | Fax #: | Phone #:

Name of insured: | City: | State: | ZIP: | E-mail: | Policy #: | Group/Policy #:

Primary insurance company: | Phone #: | Fax #: | Phone #:

Name of insured: | City: | State: | ZIP: | E-mail: | Policy #: | Group/Policy #:

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: | Degree:

DEA #: | NPI:

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

Name of facility: | Specialty: | Tax ID #: | State license #:

Office contact (name and phone):

Primary address: | City: | State: | ZIP: | E-mail:

Date: _____

John Doe MD

For the patient indicated on this form, please indicate whether:

1. You have reviewed pretreatment 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 pretreatment negative pregnancy test. ☐ Yes ☐ No

☐ Tracleer 62.5 mg (66215-0101-06) Refills #: _____

☐ Tracleer 125 mg (66215-0102-06) Refills #: _____ Dispense as Written

Directions for use:

John Doe MD

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 bosentan (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   - –Reviewed pretreatment 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' prescriptions annually by completing and submitting a new form for patients continuing therapy.

Prescriber Certification

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 bosentan (including the risks of teratogenicity and hepatotoxicity) with my patients prior to prescribing Tracleer.
   - –Reviewed pretreatment 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' prescriptions annually by completing and submitting a new form for patients continuing therapy.

Prescription Information

BEFORE SIGNING, SEE IMPORTANT SAFETY INFORMATION ON BACK.

Tracleer® BOSENTAN TABLETS

3 Monitor liver function and pregnancy test results monthly

Safe 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 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.

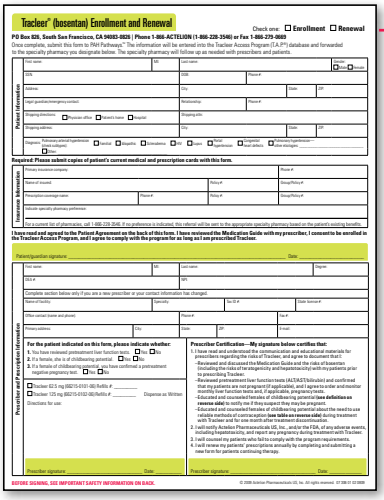
†If Tracleer is reintroduced it should be at the starting dose; aminotransferase levels should be checked within 3 days.

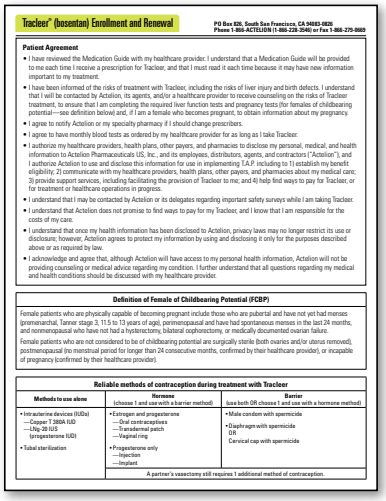
Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Please see accompanying full prescribing information.

4 Renew Tracleer enrollment annually

In order to continue your patients on Tracleer, you must return to the start of the process (step 1) annually and review the educational materials about Tracleer benefits and risks with your patients. You must also complete steps 2 and 3, including obtaining patient consent and signing both prescriber signature sections of the Tracleer Enrollment and Renewal form. The form gives you a choice at the top of whether your patient is new to Tracleer (enrollment) or continuing on therapy (renewal). Check the renewal box, complete the form, and fax it to PAH Pathways™ at 1-866-279-0669. Keep a copy for your records.





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

- In the Tracleer pivotal clinical trials, 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.
- Because these changes are a marker for potential serious liver injury, liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter.
- Elevations in aminotransferases require close attention.
- 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 liver injury may be more difficult.
- It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.
  - Changes in aminotransferases may occur early or late in treatment.
  - There have been rare postmarketing reports of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring; the contribution of Tracleer could not be excluded.
- 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.
  - For patients whose **monthly** LFTs are >3 × ULN, close monitoring and either dose reduction or treatment cessation are necessary.

Please see accompanying full prescribing information.

Safety profile: Pregnancy warnings

Pregnancy must be excluded and prevented

- Tracleer is likely to cause major birth defects if used by pregnant females, based on animal data.
- To prevent pregnancy, females of childbearing potential must use 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.
- Monthly pregnancy tests should be obtained.
- Please remember that a patient receiving Tracleer can transition into a female of childbearing potential during the course of therapy.

Female of childbearing potential

- 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

- 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.

<table>
<tr><th>Methods to use alone</th><th>Hormone
(choose 1 and use with a barrier method)</th><th>Barrier
(use both OR choose 1 and use with a hormone method)</th></tr>
<tr><td rowspan="2">• Intrauterine devices (IUDs)
—Copper T 380A IUD
—LNg-20 IUS (progesterone IUD)
• Tubal sterilization</td><td>• Estrogen and progesterone
—Oral contraceptives
—Transdermal patch
—Vaginal ring
• Progesterone only
—Injection
—Implant</td><td>• Male condom with spermicide
• Diaphragm with spermicide
OR
Cervical cap with spermicide</td></tr>
<tr><td colspan="2">A partner's vasectomy still requires 1 additional method of contraception.</td></tr>
</table>

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

Safety profile when administered with other standard PAH medications in Study 351, BREATHE-1, and EARLY

- 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]

Fluid retention

- 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.

Effect on sperm count

- 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

Pulmonary veno-occlusive disease (PVOD)

- If signs of pulmonary edema occur when Tracleer is administered, the possibility of associated PVOD should be considered and Tracleer should be discontinued.

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

19 of 38

Adverse events

Adverse events occurring in ≥3% of patients treated with Tracleer and more frequently than the placebo group*[1]

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%
Liver function test abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	-	-

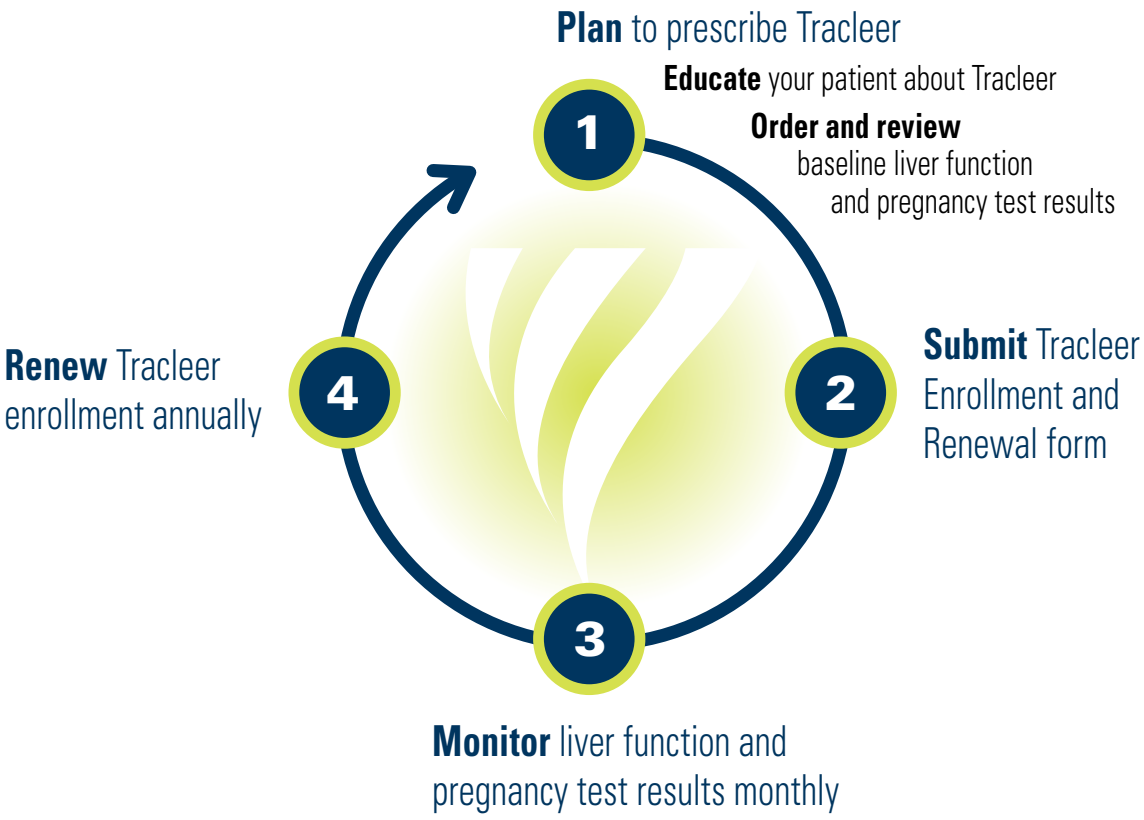
*Investigator-reported safety data obtained from 430 patients in placebo-controlled trials in PAH at doses of 125 mg BID or 250 mg BID.

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. 2009. **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 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.

PAHPathways™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

Tracleer®
BOSENTAN TABLETS

www.TRACLEER.com

[Month Day, Year]

Dear Valued Tracleer Prescriber:

Actelion has updated the way patients are enrolled for and maintained on Tracleer therapy. Because of the risks associated with Tracleer, including hepatotoxicity and teratogenicity, Actelion has updated the process of enrollment and renewal in the Tracleer Access Program (T.A.P.®) to ensure the ongoing safe use of Tracleer. While it is very similar to what you are accustomed to, there are some important changes.

What changes should you expect when prescribing Tracleer?

Renewal of Tracleer enrollment is now required annually. This entails a thorough review and discussion with your patients of the Medication Guide and the risks associated with Tracleer, and the submission of a completed Enrollment and Renewal form.

Prescriber certification is now required with each prescription (both initial enrollments and annual renewals). This involves confirming on the Tracleer Enrollment and Renewal form that you are aware of and have fulfilled essential steps that will help ensure the ongoing safe use of Tracleer.

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 (see definition and table on reverse side) 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. Please remember that a patient receiving Tracleer can transition into a female of childbearing potential during the course of therapy.

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.

Enclosed is the new Essentials kit, which includes everything you need to enroll and renew your patients in T.A.P. The kit contains the following:

- Prescriber Essentials guide, with updated package insert
- New Tracleer Enrollment and Renewal forms
- Patient Essentials guides, which include the updated Medication Guide

Also enclosed is a copy of the letter that patients currently taking Tracleer will receive explaining the updated process.

Please see important safety information on the next page.

ACTELION

Definition of female of childbearing potential

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

- 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.

<table>
<tr><th>Methods to use alone</th><th>Hormone
(choose 1 and use with a barrier method)</th><th>Barrier
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OR
Cervical cap with spermicide</td></tr>
<tr><td colspan="2">A partner's vasectomy still requires 1 additional method of contraception.</td></tr>
</table>

IMPORTANT SAFETY INFORMATION

Because of the associated risks, Tracleer may be prescribed only through the Tracleer Access Program. **Potential for serious liver injury** (including, after prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring)—Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter. **High potential for major birth defects—**Pregnancy must be excluded and prevented through the use of reliable forms of birth control; monthly pregnancy tests should be obtained.
Contraindicated for use with cyclosporine A and glyburide.

Please see accompanying full prescribing information.

Questions? Actelion is committed to making your transition to this updated process as smooth as possible. If you have any questions, please contact your local Tracleer representative or call PAH Pathways, which administers T.A.P., toll-free at 1-866-ACTELION (1-866-228-3546).

Sincerely,

Kirk Taylor, MD
Senior Vice President, Medical
Actelion Pharmaceuticals US

Tracleer® BOSENTAN TABLETS

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 see accompanying full prescribing information, including **BOXED WARNING** and Medication Guide.*

The Medication Guide starts on page 6 and is also enclosed in the back pocket.

PAHPathways™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

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 if liver problems are not found early. Tracleer is likely to cause serious birth defects if taken during pregnancy.

To start treatment with Tracleer, you must review essential safety information with your healthcare provider, complete a Tracleer Enrollment and Renewal form, and agree to have important monthly tests. To continue therapy with Tracleer, you and your healthcare provider will renew your enrollment each year by completing another form.

As a patient taking Tracleer, you may be contacted periodically to provide feedback on your understanding of the risks associated with the use of Tracleer, and the importance of monthly liver and, if applicable, pregnancy testing.

Service and support essentials

Tracleer Access Program (T.A.P.®)

Because of the risks 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 and Renewal 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 5.

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

*Please see full prescribing information, including **BOXED WARNING** and Medication Guide, in the back pocket of this booklet.*

Starting, taking, and renewing Tracleer

STARTING TRACLEER

Review the Medication Guide with your healthcare provider

Go for pretreatment liver function and pregnancy tests

Complete the Tracleer Enrollment and Renewal form with your healthcare provider

TAKING TRACLEER

Receive Tracleer from your specialty pharmacy

Go for monthly liver function and pregnancy tests

RENEWING TRACLEER

Renew Tracleer enrollment with your healthcare provider every year

Tracleer® BOSENTAN TABLETS

1 Starting Tracleer

Review the Medication Guide with your healthcare provider

The Medication Guide starts on page 6 of this booklet, and it is also in the back pocket. It covers important facts about Tracleer that you must understand before you start therapy, including the risks of liver injury and serious birth defects. Talk with your healthcare provider if you have any questions.

Go for your pretreatment 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 and Renewal 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 and Renewal 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 have been informed of the risks of treatment with Tracleer, including the risks of liver injury 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 I may be contacted by Actelion or its delegates regarding important safety surveys while I am taking Tracleer.
- I understand that Actelion does not promise to find ways to pay for my Tracleer, and I know that I am responsible for the costs of my care.
- 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.

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, which starts on page 6 of this guide.

3 Renewing Tracleer

Renew Tracleer enrollment with your healthcare provider every year

In order to continue on Tracleer, you must start over again every year by reviewing the Medication Guide and completing the Tracleer Enrollment and Renewal form with your healthcare provider (step 1).

*Please see full prescribing information, including **BOXED WARNING** and Medication Guide, in the back pocket of this booklet.*

Tracleer® BOSENTAN TABLETS

Medication guide

Tracleer (tra-KLEER)
(bosentan) Tablets

Read the Medication Guide that comes with Tracleer before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

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

  — 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.

Please see full prescribing information, including ***BOXED WARNING,*** *in the back pocket of this booklet.*

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 2 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. These methods can be used alone.**

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.

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.

Tracleer is only:

- prescribed by healthcare providers who are enrolled in T.A.P.
- available to people who understand and agree to enroll in T.A.P.

It is not known if Tracleer is safe and works in children below 12 years of age.

Medication guide (continued)

Who should not take Tracleer?

Do not take Tracleer if you:

- **are pregnant, plan to become pregnant, or become pregnant during Tracleer treatment. Tracleer can cause serious birth defects.** All females should read the **birth defects** section of "What is the most important information I should know about Tracleer?"
- have a blood test that shows possible liver injury.
- take one of these medicines:
  - — cyclosporine A used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants
  - — glyburide used for diabetes
- are allergic to any of the ingredients in Tracleer. See the end of this Medication Guide for a list of the ingredients in Tracleer. If you have a rash, hives or your lips swell after taking Tracleer, it may be a sign of allergy. You should stop taking your Tracleer and talk to your healthcare provider.

What should I tell my healthcare provider before taking Tracleer?

Tracleer may not be right for you. **Tell your healthcare provider about all your medical conditions, including if you:**

- **have liver problems.**
- **are breast-feeding or plan to breast-feed.** It is not known if Tracleer passes into your milk. You and your healthcare provider should decide if you will take Tracleer or breast-feed. You should not do both.

Please see full prescribing information, including ***BOXED WARNING,*** *in the back pocket of this booklet.*

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Tracleer and other medicines may affect how each other works and cause side effects. Especially tell your healthcare provider if you take:

- hormone-based birth control, such as pills, shots, patches, and implants. These birth control methods may not work as well when taken with Tracleer.
- simvastatin or other "-statin" medicines used to lower cholesterol
- rifampin used for tuberculosis
- tacrolimus used to prevent rejection of liver or kidney transplant
- ketoconazole, fluconazole, itraconazole, or voriconazole used for fungal infections
- warfarin sodium used to prevent blood clots
- ritonavir used to treat HIV

There may be more than one brand name medicine. Ask your healthcare provider if you are not sure if your medicine is one that is listed above.

How should I take Tracleer?

Your healthcare provider will give you detailed information about T.A.P.

- Tracleer will be mailed to you by a specialty pharmacy. You will only receive a 30-day supply of Tracleer at one time.
- Take Tracleer exactly as prescribed.
- Your healthcare provider will tell you how much Tracleer to take and when to take it.
- In most cases, you will take 1 tablet in the morning and 1 in the evening.
- You can take Tracleer with or without food.
- If you take more than the prescribed dose of Tracleer, call your healthcare provider right away.
- If you miss a dose of Tracleer, take your tablet as soon as you remember. Do not take 2 doses at the same time. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time.
- Do not stop taking Tracleer unless your healthcare provider tells you to. Suddenly stopping your treatment may cause your symptoms to get worse. If you need to stop taking Tracleer, speak with your healthcare provider about the right way to stop.

Tracleer® BOSENTAN TABLETS

Medication guide (continued)

What are the possible side effects of Tracleer?

Tracleer can cause serious side effects, including:

- **See "What is the most important information I should know about Tracleer?"**
- **Fluid retention and swelling of your ankles and legs.** Tracleer can cause your body to hold too much water, and you may get swelling of your ankles and legs. Tell your healthcare provider if you have swelling of your ankles and legs that happens either with or without weight gain, or if you have more trouble with your breathing than normal. Your healthcare provider will look for the cause of this.
- **Lower sperm count.** Some men who take Tracleer may have lower sperm counts. This may affect your ability to father a child. Tell your healthcare provider if fertility is a concern for you.
- **Low red blood cell levels (anemia).** Your healthcare provider will do blood tests to check your red blood cells during treatment with Tracleer.

The most common side effects of Tracleer are:

- respiratory tract infection
- headache
- fainting
- flushing
- low blood pressure
- inflamed nose passages (sinusitis)
- joint pain
- irregular heartbeats

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Tracleer. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Tracleer?

- Store Tracleer at 68°F to 77°F (20°C-25°C).
- **Keep Tracleer and all medicines out of the reach of children.**

Please see full prescribing information, including ***BOXED WARNING,*** *in the back pocket of this booklet.*

General information about Tracleer

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Tracleer for a condition for which it was not prescribed. Do not give Tracleer to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Tracleer. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Tracleer that is written for health professionals. For more information, go to www.TRACLEER.com or call 1-866-228-3546.

What are the ingredients in Tracleer?

Active ingredient: bosentan.

Inactive ingredients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, ethylcellulose.

Reliable methods of contraception during treatment with Tracleer

<table>
<tr><th>Methods to use alone</th><th>Hormone
(choose 1 and use with a barrier method)</th><th>Barrier
(use both OR choose 1 and use with a hormone method)</th></tr>
<tr><td rowspan="2">• Intrauterine devices (IUDs)
—Copper T 380A IUD
—LNg-20 IUS (progesterone IUD)
• Tubal sterilization</td><td>• Estrogen and progesterone
—Oral contraceptives
—Transdermal patch
—Vaginal ring
• Progesterone only
—Injection
—Implant</td><td>• Male condom with spermicide
• Diaphragm with spermicide
OR
Cervical cap with spermicide</td></tr>
<tr><td colspan="2">A partner's vasectomy still requires 1 additional method of contraception.</td></tr>
</table>

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised August 2009

Tracleer® BOSENTAN TABLETS

Starting, taking, and renewing Tracleer

STARTING TRACLEER

Review the Medication Guide with your healthcare provider

1

Go for pretreatment liver function and pregnancy tests

Complete the Tracleer Enrollment and Renewal form with your healthcare provider

2

TAKING TRACLEER

Receive Tracleer from your specialty pharmacy

Go for monthly liver function and pregnancy tests

3

RENEWING TRACLEER

Renew Tracleer enrollment with your healthcare provider 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 full prescribing information, including **BOXED WARNING** and Medication Guide, in the back pocket of this booklet.*

PAHPathways™
ACTELION SERVICES & SUPPORT

Tracleer Access Program (T.A.P.®)

BOSENTAN TABLETS

ACTELION

www.TRACLEER.com