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 (1-866-222-3546).

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)

- Screening/Tracleer enrollment
- Patient discussion of Tracleer
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

<table>
<thead>
<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>
</thead>
<tbody>
<tr>
<td>• Intrauterine devices (IUDs)</td>
<td>• Estrogen and progesterone</td>
<td>• Male condom with spermicide</td>
</tr>
<tr>
<td>— Copper T 380A IUD</td>
<td>— Oral contraceptives</td>
<td>— Diaphragm with spermicide OR</td>
</tr>
<tr>
<td>— LNG-20 IUS (progesterone IUD)</td>
<td>— Transdermal patch</td>
<td>— Cervical cap with spermicide</td>
</tr>
<tr>
<td>• Tubal sterilization</td>
<td>• Progesterone only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>— Injection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>— Implant</td>
<td></td>
</tr>
</tbody>
</table>

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

Reference ID: 3334175

Page 37
≤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 x 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

<table>
<thead>
<tr>
<th>T.A.P. Prescribing Materials</th>
<th>T.A.P. Hospital Certification</th>
<th>T.A.P. Patient Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracleer Full Prescribing Information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracleer Enrollment for Patients and Prescribers form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracleer Renewal form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriber Certification form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescriber Essentials Guide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dear Prescriber Letter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Essentials Guide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T.A.P. Hospital Certification form</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dear Hospital Letter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracleer Medication Guide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient Essentials Guide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 further 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

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

/s/

MARY R SOUTHWORTH
07/01/2013