Please see accompanying full prescribing information, including BOXED WARNING about hepatotoxicity and teratogenicity.
Introduction to the essentials

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

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

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

Program overview

Tracleer Access Program (T.A.P.)

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

As a certified prescriber of Tracleer, you may be contacted periodically to provide feedback regarding the effectiveness of T.A.P. to further ensure the ongoing safe use of Tracleer. T.A.P. is administered by PAH Pathways®. You can reach PAH Pathways by calling toll-free at 1-866-ACTELION (1-866-228-3546). For more information about T.A.P. and the requirements of the program, please visit www.TracleerREMS.com.

Certified specialty pharmacies

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

4 ESSENTIAL steps to enrollment and renewal

1. Plan to prescribe Tracleer
2. Educate your patient about Tracleer
3. Order and review liver function and pregnancy test results monthly
4. Submit Tracleer Enrollment for Patients and Prescribers form

Renew Tracleer enrollment annually

Monitor liver function and pregnancy test results monthly
Plan to prescribe Tracleer

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

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

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

You must also agree to:

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

The Patient Essentials guide is available to help you discuss the steps of Tracleer enrollment and renewal with your patients.

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

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.
Monitor liver function and pregnancy test results monthly

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

Tracleer aminotransferase (ALT/AST) management

<table>
<thead>
<tr>
<th>ALT/AST level</th>
<th>Treatment and monitoring recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3 x ULN*</td>
<td>Continue to monitor; no change in monitoring schedule or dosage</td>
</tr>
<tr>
<td>&gt;3 to ≤5 x ULN</td>
<td>Confirm by another test; if confirmed, reduce the dose or interrupt treatment and monitor LFT levels every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Continue or reintroduce Tracleer if levels return to pretreatment levels</td>
</tr>
<tr>
<td>&gt;5 to ≤8 x ULN</td>
<td>Confirm by another test; if confirmed, stop therapy; monitor LFTs at least every 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Consider reintroduction of therapy if LFTs return to pretreatment levels</td>
</tr>
<tr>
<td>&gt;8 x ULN</td>
<td>Stop therapy; do not reintroduce</td>
</tr>
</tbody>
</table>

*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.

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

Liver enzyme elevations: experience and management

- Use of Tracleer should generally be avoided in patients with elevated aminotransferases (>3 × ULN) at baseline because monitoring for hepatotoxicity may be more difficult.
- 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.

Safety profile: Pregnancy warnings

Pregnancy must be excluded and prevented

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

Female of childbearing potential

- 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 inserted.

<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 — Oral contraceptives — Transdermal patch — Vaginal ring</td>
<td>• Male condom with spermicide — Diaphragm with spermicide OR — Cervical cap with spermicide</td>
</tr>
<tr>
<td>— Copper T 380A IUD — LNG-20 IUS (progesterone IUD)</td>
<td>• Progestrone only — Injection — Implant</td>
<td></td>
</tr>
<tr>
<td>• Tubal sterilization</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A partner’s vasectomy still requires 1 additional method of contraception.
Safety profile: Warnings, precautions, adverse events, and drug interactions

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

- Patients receiving Tracleer continued other medications, including anticoagulants, digoxin, diuretics, and vasodilators such as calcium channel blockers and ACE inhibitors.1,2
- Patients receiving epoprostenol within 3 months of study screening were ineligible for participation.2,3
- In the EARLY trial, both the Tracleer group and the placebo group included some patients on sildenafil at baseline (Tracleer, n=14; placebo, n=18).4

Fluid retention1

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

Pulmonary veno-occlusive disease (PVOD)1

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

Decreased sperm counts1

- 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 hemoglobin1

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

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

<table>
<thead>
<tr>
<th>Adverse events1</th>
<th>Adverse events occurring in ≥3% of patients treated with Tracleer and more frequently than the placebo group1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>Tracleer (n=258)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>56</td>
</tr>
<tr>
<td>Headache</td>
<td>39</td>
</tr>
<tr>
<td>Edema</td>
<td>28</td>
</tr>
<tr>
<td>Chest pain</td>
<td>13</td>
</tr>
<tr>
<td>Syncope</td>
<td>12</td>
</tr>
<tr>
<td>Retching</td>
<td>10</td>
</tr>
<tr>
<td>Hypotension</td>
<td>10</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>9</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9</td>
</tr>
<tr>
<td>Serum aminotransferases abnormal</td>
<td>9</td>
</tr>
<tr>
<td>Palpitations</td>
<td>9</td>
</tr>
<tr>
<td>Aneemia</td>
<td>8</td>
</tr>
</tbody>
</table>

*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 interactions1

- 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.

4 ESSENTIAL steps to success

1. **Plan** to prescribe Tracleer
2. **Educate** your patient about Tracleer
3. **Order and review** liver function and pregnancy test results
4. **Renew** Tracleer enrollment annually

Submit Tracleer Enrollment for Patients and Prescribers form

Monitor liver function and pregnancy test results monthly

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

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