IMPORTANT PRESCRIBING INFORMATION

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

Dear Tracleer Prescriber,

Actelion Pharmaceuticals US, Inc. (Actelion), would like to inform you of important changes in the requirements for dispensing Tracleer in the inpatient setting, and the introduction of blister pack dosing units for hospital use. Because of the risks of hepatotoxicity and teratogenicity, Tracleer has a BOXED WARNING and is available only through a restricted program called the Tracleer Access Program (T.A.P.), which is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, pharmacies, and hospitals must enroll in the program. For more information about T.A.P. and the requirements of the program, please see www.TracleerREMS.com or call 1-866-ACTELION (1-866-228-3546).

PROGRAM CHANGES

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

Initiating Tracleer in a Certified Hospital
Hospitals must be certified before initiating use of Tracleer in an inpatient setting.

• Tracleer may be dispensed only to inpatients who are under the supervision and care of a healthcare provider who has been certified in T.A.P.
  – Complete the Tracleer Prescriber Certification form confirming you are aware of and have fulfilled essential steps that will help ensure the ongoing safe use of Tracleer.
  – Send the completed Tracleer Prescriber Certification form to PAH Pathways®, the administrator of T.A.P., by fax at 1-866-279-0669. The information will be entered in the T.A.P. database.

• Ensure your patient has been enrolled in the Tracleer Access Program prior to discharge from the hospital.
  – Complete the Tracleer Enrollment for Patients and Prescribers form with your patient and send it to PAH Pathways by fax at 1-866-279-0669.
  – PAH Pathways will then work with a certified specialty pharmacy to ensure your patient receives Tracleer in the outpatient setting.

• Ensure baseline liver monitoring has been conducted and pregnancy has been excluded in females of childbearing potential.

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

Other Changes to the Tracleer Access Program (T.A.P.)
The Tracleer Access Program has further been updated to include the following:

• Updates to the Tracleer Enrollment for Patients and Prescribers form.
• A new stand-alone Prescriber Certification form. Prescribers may now certify either by completing the Tracleer Enrollment for Patients and Prescribers form or by completing the new Prescriber Certification form.
• A new stand-alone Tracleer Renewal form. Annual patient re-enrollment may now be done by certified prescribers only (without requiring patient consent), by completing the Tracleer Renewal form.

What Has Not Changed with the Tracleer Access Program
• Because of the risks of hepatotoxicity and teratogenicity, Tracleer continues to be available only through a restricted distribution program (T.A.P.).
Tracleer Access Program (T.A.P.)

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

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

**Indication**

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

**Important Safety Information**

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

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

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

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

**Contraindications**

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

**Adverse Event Reporting**

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

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

Sincerely,

[Signature]

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