IMPORTANT PRESCRIBING INFORMATION

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

Dear Hospital,

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

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

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

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

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

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

Blister Packs for Hospital Use Only
The “How Supplied” section of the Tracleer full prescribing information has been revised to include the addition of 30-unit blister packs for hospital use only.

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

Hepatotoxicity: Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer. In a setting of close monitoring, rare cases of liver failure and unexplained hepatic cirrhosis were observed after prolonged treatment. In general, avoid using Tracleer in patients with elevated aminotransferases (≥3 × ULN). Measure liver aminotransferases prior to initiation of treatment and then monthly. Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.
**Teratogenicity.** Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy. Exclude pregnancy before and during treatment. To prevent pregnancy, females of childbearing potential must use 2 reliable forms of contraception during treatment and for 1 month after stopping Tracleer unless the patient has a tubal sterilization or Copper T 380A IUD or LNG-20 IUS inserted, in which case no other contraception is needed. Obtain monthly pregnancy tests. Hormonal contraceptives may not be reliable when Tracleer is co-administered.

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

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

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

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

Sincerely,

[Signature]

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