HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TRACLEER® safely and effectively. See full prescribing information for TRACLEER.

TRACLEER® (bosentan) tablets, for oral use
Initial U.S. Approval: 2001

WARNING: RISKS OF HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

See full prescribing information for complete boxed warning.

Tracleer is available only through a restricted distribution program called the Tracleer REMS Program because of these risks (5.2):
Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer (5.1).

- **Measure liver aminotransferases prior to initiation of treatment and then monthly (5.1).**
- **Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 x ULN (2.2, 5.1).**

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy (4.1, 8.1).

- **Must exclude pregnancy before and during treatment (4.1, 8.1).**
- **To prevent pregnancy, females of reproductive potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer (4.1, 8.1).**

RECENT MAJOR CHANGES

Boxed Warning	12/2015
Dosage and Administration (2, 2.3)	12/2015
Contraindications (4.1, 4.4)	10/2016
Warnings and Precautions (5.2)	12/2015

INDICATIONS AND USAGE

Tracleer is an endothelin receptor antagonist 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%) (1.1).

Considerations for use:
Consider whether benefits offset the risk of hepatotoxicity in WHO Class II patients. Early hepatotoxicity may preclude future use as disease progresses (1.1).

DOSAGE AND ADMINISTRATION

- Initiate at 62.5 mg twice daily with or without food for 4 weeks, and then increase to 125 mg twice daily (2.1).
- Patients with low body weight (<40 kg) and >12 years old: Initial and maintenance dose is 62.5 mg twice daily (2.4).
- Reduce the dose and closely monitor patients developing aminotransferase elevations >3 X ULN (2.2).
- Discontinue Tracleer 36 hours prior to initiation of ritonavir. Patients on ritonavir: Initiate Tracleer at 62.5 mg once daily or every other day (2.5).

DOSAGE FORMS AND STRENGTHS

- Tablet: 62.5 mg and 125 mg (3)

CONTRAINDICATIONS

- Pregnancy (4.1)
- Use with Cyclosporine A (4.2)
- Use with Glyburide (4.3)
- Hypersensitivity (4.4)

WARNINGS AND PRECAUTIONS

- Pre-existing hepatic impairment: Avoid use in moderate and severe impairment (5.3).
- Fluid retention: May require intervention (5.4).
- Pulmonary veno-occlusive disease *(*PVOD*)*: If signs of pulmonary edema occur, consider the diagnosis of associated PVOD and consider discontinuing Tracleer (5.5)
- Decreased sperm counts (5.6)
- Decreases in hemoglobin and hematocrit: Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter (5.7).

ADVERSE REACTIONS

Common adverse reactions (≥3% more than placebo) are respiratory tract infection and anemia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Actelion at 1-866-228-3546 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Hormonal contraceptives: Tracleer use decreases contraceptive exposure and reduces effectiveness (7.2).
- Simvastatin and other CYP3A-metabolized statins: Combination use decreases statin exposure and may reduce efficacy (7.6).
- Rifampin: Alters bosentan exposure. Monitor hepatic function weekly for 4 weeks, followed by normal monitoring (7.7).

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Choose breastfeeding or Tracleer (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide **Revised: 10/2016**

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: RISKS OF HEPATOTOXICITY and EMBRYO-FETAL TOXICITY

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer REMS Program. The Tracleer REMS Program 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. *[see Warnings and Precautions (5.2)].*

Hepatotoxicity

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. Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly *[see Dosage and Administration (2.2), Warnings and Precautions (5.1)]*. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with Tracleer in patients with multiple comorbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction *[see Dosage and Administration (2.2)]*.

Elevations in aminotransferases require close attention *[see Dosage and Administration (2.2)]*. Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring for hepatotoxicity may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the reintroduction of Tracleer in these circumstances.

Embryo-Fetal Toxicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data *[see Use in Specific Populations (8.1)]*. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of reproductive potential must use two reliable methods of contraception unless the patient has an intrauterine device (IUD) or tubal sterilization, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving Tracleer *[see Drug Interactions (7.2)]*. Obtain monthly pregnancy tests.

1. INDICATIONS AND USAGE

1.1 Pulmonary Arterial Hypertension

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%) *[see Clinical Studies (14.1)]*.

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.

2. DOSAGE AND ADMINISTRATION

Healthcare professionals who prescribe Tracleer must enroll in the Tracleer REMS Program and must comply with the required monitoring to minimize the risks associated with Tracleer *[see Warnings and Precautions (5.2)]*.

2.1 Adult Dosage

Initiate treatment at 62.5 mg twice daily for 4 weeks and then increase to the maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of hepatotoxicity.

Tracleer should be administered in the morning and evening with or without food.

2.2 Dosage Adjustments for Patients Developing Aminotransferase Elevations

Measure liver aminotransferase levels prior to initiation of treatment and then monthly. If aminotransferase levels increase, revise the monitoring and treatment plan. The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during therapy with Tracleer. Discontinue Tracleer if liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN. There is no experience with the reintroduction of Tracleer in these circumstances.

Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations >3 x ULN

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values, continue or reintroduce the treatment as appropriate*.
> 5 and ≤ 8 x ULN	Confirm by another aminotransferase test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values, consider reintroduction of the treatment*.
> 8 x ULN	Treatment should be stopped and reintroduction of Tracleer should not be considered. There is no experience with reintroduction of Tracleer in these circumstances.

* If Tracleer is re-introduced it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

2.3 Pregnancy Testing in Females of Reproductive Potential

Initiate treatment with Tracleer in females of reproductive potential only after a negative pregnancy test. Obtain monthly pregnancy test during treatment *[see Use in Specific Populations (8.1)]*.

2.4 Patients with Low Body Weight

In patients with a body weight below 40 kg but who are over 12 years of age, the recommended initial and maintenance dose is 62.5 mg twice daily. There is limited information about the safety and efficacy of Tracleer in children between the ages of 12 and 18 years *[see Use in Specific Populations (8.4)]*.

2.5 Use with Ritonavir

Coadministration of Tracleer in Patients on Ritonavir

In patients who have been receiving ritonavir for at least 10 days, start Tracleer at 62.5 mg once daily or every other day based upon individual tolerability *[see Drug Interactions (7.5)]*.

Coadministration of Ritonavir in Patients on Tracleer

Discontinue use of Tracleer at least 36 hours prior to initiation of ritonavir. After at least 10 days following the initiation of ritonavir, resume Tracleer at 62.5 mg once daily or every other day based upon individual tolerability *[see Dosage and Administration (2.7), Drug Interactions (7.5)]*.

2.6 Use in Patients with Pre-existing Hepatic Impairment

Tracleer should generally be avoided in patients with moderate or severe liver impairment. Initiation of Tracleer should generally be avoided in patients with elevated aminotransferases >3 x ULN. No dose adjustment is required in patients with mildly impaired liver function *[see Warnings and Precautions (5.3), Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*.

2.7 Treatment Discontinuation

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. Nevertheless, to avoid the potential for clinical deterioration, gradual dose reduction (62.5 mg twice daily for 3 to 7 days) should be considered.

3. DOSAGE FORMS AND STRENGTHS

62.5 mg and 125 mg film-coated, tablets for oral administration.

62.5 mg tablets: round, biconvex, orange-white tablets, embossed with identification marking “62,5”

125 mg tablets: oval, biconvex, orange-white tablets, embossed with identification marking “125”

4. CONTRAINDICATIONS

4.1 Pregnancy

Use of Tracleer is contraindicated in females who are or may become pregnant. To prevent pregnancy, females of reproductive potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer . *[see Boxed Warning, Warnings and Precautions (5.2), Drug Interactions (7.2), Use in Specific Populations (8.1)]*.

4.2 Use with Cyclosporine A

Coadministration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Tracleer and cyclosporine A is contraindicated *[see Drug Interactions (7.3)]*.

4.3 Use with Glyburide

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore coadministration of glyburide and Tracleer is contraindicated *[see Drug Interactions (7.4)]*.

4.4 Hypersensitivity

Tracleer is contraindicated in patients who are hypersensitive to bosentan or any component of the product. Observed reactions include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), anaphylaxis, rash and angioedema *[see Adverse Reactions (6.2), Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

Elevations in ALT or AST by more than 3 x ULN were observed in 11% of Tracleer-treated patients (n = 658) compared to 2% of placebo-treated patients (n = 280). Three-fold increases were seen in 12% of 95 pulmonary arterial hypertension (PAH) patients on 125 mg twice daily and 14% of 70 PAH patients on 250 mg

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