

**TRACLEER- bosentan tablet, film coated**  
**Actelion Pharmaceuticals US, Inc.**

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**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  $\geq 2 \times$  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  $>3 \times$  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 ( $\geq 3\%$  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](http://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**

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## **FULL PRESCRIBING INFORMATION**

## **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 ( $> 3 \times$  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  $\geq 2 \times$  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  $>3 \times \text{ULN}$  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  $\geq 2 \times \text{ULN}$ . There is no experience with the reintroduction of Tracleer in these circumstances.

**Table 1: Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Elevations  $>3 \times \text{ULN}$**

ALT/AST levels	Treatment and monitoring recommendations
$> 3$ and $\leq 5 \times \text{ULN}$	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 $\leq 8 \times \text{ULN}$	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*.
$> 8 \times \text{ULN}$	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  $>3 \times$  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  $3 \times$  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 twice daily. Eight-fold increases were seen in 2% of PAH patients on 125 mg twice daily and 7% of PAH patients on 250 mg twice daily. Bilirubin increases to  $\geq 3 \times$  ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with Tracleer. The combination of hepatocellular injury (increases in aminotransferases of  $> 3 \times$  ULN) and increases in total bilirubin ( $\geq 2 \times$  ULN) is a marker for potential serious hepatotoxicity.

Elevations of AST or ALT associated with Tracleer are dose-dependent, occur both early and late in treatment, usually progress slowly, are typically asymptomatic, and usually have been reversible after treatment interruption or cessation. Aminotransferase elevations also may reverse spontaneously while continuing treatment with Tracleer.

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly and therapy adjusted accordingly [see *Dosage and Administration (2.2)*]. 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  $\geq 2 \times$  ULN.

### 5.2 Prescribing and Distribution Program for Tracleer

Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer REMS Program. As a component of the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program. [see *Boxed Warning and Contraindications (4.1)*].

Required components of the Tracleer REMS are:

- Healthcare professionals who prescribe Tracleer must review the prescriber educational materials, enroll in the Tracleer REMS Program and comply with its requirements.
- Healthcare professionals must (1) review serum aminotransferases (ALT/AST) and bilirubin, and agree to order and monitor these tests monthly; and (2) for females of reproductive potential, confirm that the patient is not pregnant, and agree to order and monitor pregnancy tests monthly.
- To receive Tracleer, all patients must understand the risks and benefits, complete a patient enrollment form.
- Pharmacies that dispense Tracleer must enroll in the program and agree to comply with the Tracleer REMS Program requirements.

Further information about Tracleer and the Tracleer REMS Program is available at [www.Tracleerrem.com](http://www.Tracleerrem.com) or 1-866-228-3546.

### 5.3 Patients with Pre-existing Hepatic Impairment

Tracleer is not recommended in patients with moderate or severe liver impairment. In addition, initiation of Tracleer should generally be avoided in patients with elevated aminotransferases ( $> 3 \times \text{ULN}$ ) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult [see *Boxed Warning, Dosage and Administration (2.5) Use in Specific Populations (8.6)*].

#### **5.4 Fluid Retention**

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of Tracleer and other endothelin receptor antagonists. In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients

In addition, there have been numerous postmarketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

If clinically significant fluid retention develops, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as Tracleer or underlying heart failure, and the possible need for treatment or discontinuation of Tracleer. [see *Adverse Reactions (6.1) and Clinical Studies (14.2)*].

#### **5.5 Pulmonary Veno-Occlusive Disease**

Should signs of pulmonary edema occur, consider the possibility of associated pulmonary veno-occlusive disease and consider whether Tracleer should be discontinued.

#### **5.6 Decreased Sperm Counts**

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 [see *Adverse Reactions (6.1), Nonclinical Toxicology (13.1)*].

#### **5.7 Decreases in Hemoglobin and Hematocrit**

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment [see *Adverse Reactions 6.1*].

### **6. ADVERSE REACTIONS**

The following important adverse reactions are described elsewhere in the labeling:

- Hepatotoxicity [see *Boxed Warning, Warnings and Precautions (5.1)*]
- Fluid retention [see *Warnings and Precautions (5.4)*]

#### **6.1 Clinical Studies Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety data on Tracleer were obtained from 13 clinical studies (9 placebo-controlled and 4 open-label) in 870 patients with pulmonary arterial hypertension and other diseases. Doses up to 8 times the currently recommended clinical dose (125 mg twice daily) were administered for a variety of durations. The exposure to Tracleer in these trials ranged from 1 day to 4.1 years (n=94 for 1 year; n=61 for 1.5 years and n=39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (n=328) to



Tracleer ranged from 1 day to 1.7 years (n=174 more than 6 months and n=28 more than 12 months).

Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on Tracleer (6%; 15/258 patients) than on placebo (3%; 5/172 patients). In this database the only cause of discontinuations > 1% and occurring more often on Tracleer was abnormal liver function.

The adverse drug events that occurred in ≥3% of the Tracleer-treated patients and were more common on Tracleer in placebo-controlled trials in pulmonary arterial hypertension at doses of 125 or 250 mg twice daily are shown in Table 2:

**Table 2. Adverse events\* occurring in ≥3% of patients treated with Tracleer 125-250 mg twice daily and more common on Tracleer in placebo-controlled studies in pulmonary arterial hypertension**

<i>Adverse Event</i>	<b>Tracleer n = 258</b>		<b>Placebo n = 172</b>	
	<b>No.</b>	<b>%</b>	<b>No.</b>	<b>%</b>
Respiratory Tract Infection	56	22%	30	17%
Headache	39	15%	25	14%
Edema	28	11%	16	9%
Chest Pain	13	5%	8	5%
Syncope	12	5%	7	4%
Flushing	10	4%	5	3%
Hypotension	10	4%	3	2%
Sinusitis	9	4%	4	2%
Arthralgia	9	4%	3	2%
Serum Aminotransferases, abnormal	9	4%	3	2%
Palpitations	9	4%	3	2%
Anemia	8	3%	-	

Combined data from Study 351, BREATHE-1 and EARLY

\* Note: only AEs with onset from start of treatment to 1 calendar day after end of treatment are included. All reported events (at least 3%) are included except those too general to be informative, and those not reasonably associated with the use of the drug because they were associated with the condition being treated or are very common in the treated population.

### **Decreased Sperm Counts**

An open-label, single arm, multicenter, safety study evaluated the effect on testicular function of Tracleer 62.5 mg twice daily for 4 weeks, followed by 125 mg twice daily for 5 months. Twenty-five male patients with WHO functional class III and IV PAH and normal baseline sperm count were enrolled. Twenty-three completed the study and 2 discontinued due to adverse events not related to testicular function. There was a decline in sperm count of at least 50% in 25% of the patients after 3 or 6 months of treatment with Tracleer. Sperm count remained within the normal range in all 22 patients with data after 6 months and no changes in sperm morphology, sperm motility, or hormone levels were observed. One patient developed marked oligospermia at 3 months and the sperm count remained low with 2 follow-up measurements over the subsequent 6 weeks. Tracleer was discontinued and after 2 months the sperm count had returned to baseline levels. Based on these findings and preclinical data from endothelin receptor antagonists, it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

### **Decreases in Hemoglobin and Hematocrit**

Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.

The overall mean decrease in hemoglobin concentration for Tracleer-treated patients was 0.9 g/dL (change to end of treatment). Most of this decrease of hemoglobin concentration was detected during the first few weeks of Tracleer treatment and hemoglobin levels stabilized by 4–12 weeks of Tracleer treatment. In placebo-controlled studies of all uses of Tracleer, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of Tracleer-treated patients and 3% of placebo-treated patients. In patients with PAH treated with doses of 125 and 250 mg twice daily, marked decreases in hemoglobin occurred in 3% compared to 1% in placebo-treated patients.

A decrease in hemoglobin concentration by at least 1 g/dL was observed in 57% of Tracleer-treated patients as compared to 29% of placebo-treated patients. In 80% of those patients whose hemoglobin decreased by at least 1 g/dL, the decrease occurred during the first 6 weeks of Tracleer treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of Tracleer-treated patients compared to 76% of placebo patients. The explanation for the change in hemoglobin is not known, but it does not appear to be hemorrhage or hemolysis.

## 6.2 Postmarketing Experience

There have been several postmarketing reports of angioedema associated with the use of Tracleer. The onset of the reported cases occurred within a range of 8 hours to 21 days after starting therapy. Some patients were treated with an antihistamine and their signs of angioedema resolved without discontinuing Tracleer.

The following additional adverse reactions have been reported during the postapproval use of Tracleer. Because these adverse reactions are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to Tracleer exposure:

Unexplained hepatic cirrhosis [*see Boxed Warning*]

Liver failure [*see Boxed Warning*]

Hypersensitivity, DRESS, and anaphylaxis [*see Contraindications (4.4)*]

Thrombocytopenia

Rash

Jaundice

Anemia requiring transfusion

Neutropenia and leukopenia

Nasal congestion

## 7. DRUG INTERACTIONS

### 7.1 Cytochrome P450 Summary

Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with Tracleer will likely lead to large increases in plasma concentrations of bosentan. Coadministration of such combinations of a CYP2C9 inhibitor plus a strong or moderate CYP3A inhibitor with Tracleer is not recommended.

Bosentan is an inducer of CYP3A and CYP2C9. Consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when Tracleer is coadministered. Bosentan had no relevant inhibitory effect on any CYP isozyme in vitro (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A). Consequently, Tracleer is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

## 7.2 Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is coadministered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer [see *Boxed Warning, Contraindications (4.1)*].

An interaction study demonstrated that coadministration of bosentan and a combination oral hormonal contraceptive produced average decreases of norethindrone and ethinyl estradiol levels of 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects.

## 7.3 Cyclosporine A

The concomitant administration of Tracleer and cyclosporine A is contraindicated [see *Contraindications (4.2)*].

During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A. Coadministration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A substrate) by approximately 50%.

## 7.4 Glyburide

An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide. Therefore, the concomitant administration of Tracleer and glyburide is contraindicated, and alternative hypoglycemic agents should be considered [see *Contraindications (4.3)*].

Coadministration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Tracleer is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A. The possibility of worsened glucose control in patients using these agents should be considered.

## 7.5 Lopinavir/Ritonavir or Other Ritonavir-containing HIV Regimens

*In vitro* data indicate that bosentan is a substrate of the Organic Anion Transport Protein (OATP), CYP3A and CYP2C9. Ritonavir inhibits OATP and inhibits and induces CYP3A. However, the impact of ritonavir on the pharmacokinetics of bosentan may largely result from its effect on OATP.

In normal volunteers, coadministration of Tracleer 125 mg twice daily and lopinavir/ritonavir 400/100 mg twice daily increased the trough concentrations of bosentan on Days 4 and 10 approximately 48-fold and 5-fold, respectively, compared with those measured after Tracleer administered alone. Therefore, adjust the dose of Tracleer when initiating lopinavir/ritonavir [see *Dosage and Administration (2.5)*].

Coadministration of bosentan 125 mg twice daily had no substantial impact on the pharmacokinetics of lopinavir/ritonavir 400/100 mg twice daily.

## 7.6 Simvastatin and Other Statins

Coadministration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A substrate), and its active  $\beta$ -hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan

were not affected. Tracleer is also expected to reduce plasma concentrations of other statins that are significantly metabolized by CYP3A, such as lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A-metabolized statins should have cholesterol levels monitored after Tracleer is initiated to see whether the statin dose needs adjustment.

### **7.7 Rifampin**

Coadministration of bosentan and rifampin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose (likely due to inhibition of OATP by rifampin), but about a 60% decrease in bosentan levels at steady-state. The effect of Tracleer on rifampin levels has not been assessed. When consideration of the potential benefits, and known and unknown risks leads to concomitant use, measure serum aminotransferases weekly for the first 4 weeks before reverting to normal monitoring.

### **7.8 Tacrolimus**

Coadministration of tacrolimus and Tracleer has not been studied in humans. Coadministration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals. Caution should be exercised if tacrolimus and Tracleer are used together.

### **7.9 Ketoconazole**

Coadministration of bosentan 125 mg twice daily and ketoconazole, a potent CYP3A inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold in normal volunteers. No dose adjustment of Tracleer is necessary, but increased effects of Tracleer should be considered.

### **7.10 Warfarin**

Coadministration of bosentan 500 mg twice daily for 6 days in normal volunteers decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A substrate) by 29 and 38%, respectively. Clinical experience with concomitant administration of Tracleer and warfarin in patients with pulmonary arterial hypertension did not show clinically relevant changes in INR or warfarin dose (baseline vs. end of the clinical studies), and the need to change the warfarin dose during the trials due to changes in INR or due to adverse events was similar among Tracleer- and placebo-treated patients.

### **7.11 Digoxin, Nimodipine, and Losartan**

Bosentan has no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan.

### **7.12 Sildenafil**

In normal volunteers, coadministration of multiple doses of 125 mg twice daily bosentan and 80 mg three times daily sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. The changes in plasma concentrations were not considered clinically relevant and dose adjustments are not necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

### **7.13 Iloprost**

In a small, randomized, double-blind, placebo-controlled study, 34 patients treated with bosentan 125 mg twice daily for at least 16 weeks tolerated the addition of inhaled iloprost (up to 5 mcg 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 mcg and the mean number of inhalations per day was 5.6.

## **8. USE IN SPECIFIC POPULATIONS**

## 8.1 Pregnancy

Pregnancy Category X: Teratogenic Effects [see Contraindications (4.1)]

Use of Tracleer is contraindicated in females who are or may become pregnant. While there are no adequate and well-controlled studies in pregnant females, animal studies show that Tracleer is likely to cause major birth defects when administered during pregnancy. Bosentan caused teratogenic effects in animals including malformations of the head, mouth, face, and large blood vessels. If Tracleer is used during pregnancy or if a patient becomes pregnant while taking Tracleer, the patient should be apprised of the potential hazard to the fetus.

Females of reproductive potential should have a negative pregnancy test before starting treatment with Tracleer. The prescriber should not dispense a prescription for Tracleer without documenting a negative urine or serum pregnancy test performed during the first 5 days of a normal menstrual period and at least 11 days after the last unprotected act of sexual intercourse. Follow-up urine or serum pregnancy tests should be obtained monthly in females of reproductive potential taking Tracleer. The patient should contact her physician immediately for pregnancy testing if onset of menses is delayed or pregnancy is suspected. If the pregnancy test is positive, the physician and patient must discuss the risks to her, the pregnancy, and the fetus.

*Contraception:* Drug interaction studies show that bosentan reduces serum levels of the estrogen and progestin in oral contraceptives. Based on these findings, hormonal contraceptives (including oral, injectable, transdermal, and implantable contraceptives) may be less effective for preventing pregnancy in patients using Tracleer and should not be used as a patient's only contraceptive method [see Drug Interactions (7.2)]. Females of reproductive potential using Tracleer must use acceptable methods of contraception during treatment with Tracleer and for 1 month after treatment with Tracleer. Patients may choose one highly effective form of contraception (intrauterine devices (IUD) or tubal sterilization) or a combination of methods (hormone method with a barrier method or two barrier methods). If a partner's vasectomy is the chosen method of contraception, a hormone or barrier method must be used along with this method. Counsel patients on pregnancy planning and prevention, including emergency contraception, or designate counseling by another healthcare provider trained in contraceptive counseling [see Boxed Warning].

Contraception should be continued until one month after completing Tracleer therapy. Females of reproductive potential using Tracleer should seek contraception counseling from a gynecologist or other expert as needed.

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/m<sup>2</sup> basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m<sup>2</sup> basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that embryo-fetal toxicity is a class effect of these drugs [see Nonclinical Toxicology (13.1)].

## 8.3 Nursing Mothers

It is not known whether bosentan is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from bosentan, a decision should be made to discontinue nursing or to discontinue Tracleer, taking into account the importance of Tracleer to the mother.

## 8.4 Pediatric Use

Safety and efficacy in pediatric patients have not been established.

## 8.5 Geriatric Use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.

## 8.6 Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure ( $C_{max}$  and AUC) of bosentan. The pharmacokinetics of Tracleer has not been evaluated in patients with severe liver impairment (Child-Pugh Class C). In patients with moderate hepatic impairment (Child-Pugh Class B), the systemic exposures to bosentan and its active metabolite increased significantly. Tracleer should generally be avoided in patients with moderate or severe liver impairment. Pharmacokinetics of bosentan was not altered in patients with mild impairment of hepatic function (Child-Pugh Class A) [see *Dosage and Administration* (2.6), *Warnings and Precautions* (5.3), *Pharmacokinetics* (12.3)].

## 8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment [see *Pharmacokinetics* (12.3)].

## 10. OVERDOSAGE

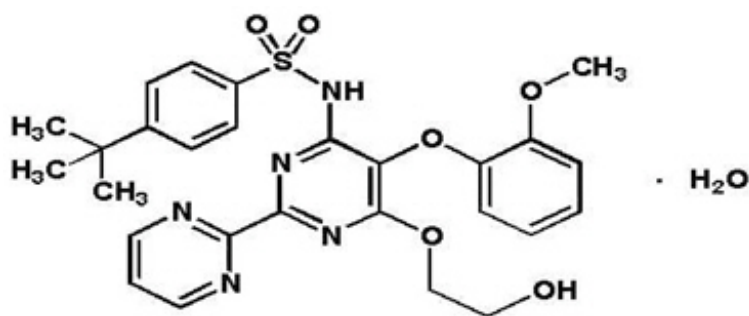
Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 and 1000 mg twice daily of bosentan were given concomitantly with cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed.

In the postmarketing period, there was one reported overdose of 10,000 mg of Tracleer taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating, and blurred vision. He recovered within 24 hours with blood pressure support.

Bosentan is unlikely to be effectively removed by dialysis due to the high molecular weight and extensive plasma protein binding.

## 11. DESCRIPTION

Tracleer is the proprietary name for bosentan, an endothelin receptor antagonist that belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. It is designated chemically as 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2']-bipyrimidin-4-yl]-benzenesulfonamide monohydrate and has the following structural formula:



Bosentan has a molecular weight of 569.64 and a molecular formula of  $C_{27}H_{29}N_5O_6S \cdot H_2O$ . Bosentan is a white to yellowish powder. It is poorly soluble in water (1.0 mg/100 mL) and in aqueous solutions at low pH (0.1 mg/100 mL at pH 1.1 and 4.0; 0.2 mg/100 mL at pH 5.0). Solubility increases at higher

pH values (43 mg/100 mL at pH 7.5). In the solid state, bosentan is very stable, is not hygroscopic and is not light sensitive.

Tracleer is available as 62.5 mg and 125 mg film-coated tablets for oral administration, and contains the following excipients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, and ethylcellulose. Each Tracleer 62.5 mg tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan. Each Tracleer 125 mg tablet contains 129.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan.

## **12. CLINICAL PHARMACOLOGY**

### **12.1 Mechanism of action**

Bosentan is a specific and competitive antagonist at endothelin receptor types ET<sub>A</sub> and ET<sub>B</sub>. Bosentan has a slightly higher affinity for ET<sub>A</sub> receptors than for ET<sub>B</sub> receptors. The clinical impact of dual endothelin blockage is unknown.

Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ET<sub>A</sub> and ET<sub>B</sub> receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease.

### **12.3 Pharmacokinetics**

#### **General**

After oral administration, maximum plasma concentrations of bosentan are attained within 3–5 hours and the terminal elimination half-life ( $t_{1/2}$ ) is about 5 hours in healthy adult subjects. The exposure to bosentan after intravenous and oral administration is about 2-fold greater in adult patients with pulmonary arterial hypertension than in healthy adult subjects.

#### **Absorption and Distribution**

The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food. The volume of distribution is about 18 L. Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

#### **Metabolism and Elimination**

Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%–20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A and possibly also of CYP2C19. Total clearance after a single intravenous dose is about 4 L/hr in patients with pulmonary arterial hypertension. Upon multiple oral dosing, plasma concentrations in healthy adults decrease gradually to 50–65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 3–5 days. Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine.

#### **Special Populations**

It is not known whether bosentan's pharmacokinetics is influenced by gender, race, or age.

#### **Hepatic Impairment**

*In vitro* and *in vivo* evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure of bosentan. In a study comparing 8 patients with mild liver impairment (Child-Pugh Class A) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan was not altered in patients with mild hepatic impairment.

In another small (N=8) pharmacokinetic study, the steady-state AUC of bosentan was on average 4.7 times higher and the active metabolite Ro 48-5033 was 12.4 times higher in 5 patients with moderately impaired liver function (Child-Pugh Class B) and pulmonary arterial hypertension associated with portal hypertension than in 3 patients with normal liver function and pulmonary arterial hypertension of other etiologies.

The pharmacokinetics of Tracleer has not been evaluated in patients with severe liver impairment (Child-Pugh Class C) [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.6)*].

### **Renal Impairment**

In patients with severe renal impairment (creatinine clearance 15–30 mL/min), plasma concentrations of bosentan were essentially unchanged and plasma concentrations of the three metabolites were increased about 2-fold compared to people with normal renal function. These differences do not appear to be clinically important.

## **13. NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

#### **Carcinogenesis and Mutagenesis**

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m<sup>2</sup> basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

#### **Reproductive and Developmental Toxicology**

Bosentan was teratogenic in rats given oral doses  $\geq 60$  mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of 60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that embryo-fetal toxicity is a class effect of these drugs.

#### **Impairment of Fertility/Testicular Function**

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m<sup>2</sup> basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day



(about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

## 14. CLINICAL STUDIES

### 14.1 Pulmonary Arterial Hypertension

#### WHO Functional Class III-IV

Two randomized, double-blind, multi-center, placebo-controlled trials were conducted in 32 and 213 patients. The larger study (BREATHE-1) compared 2 doses (125 mg twice daily and 250 mg twice daily) of Tracleer with placebo. The smaller study (Study 351) compared 125 mg twice daily with placebo. Patients had severe (WHO functional Class III–IV) pulmonary arterial hypertension: idiopathic or heritable pulmonary arterial hypertension (72%) or pulmonary arterial hypertension associated with scleroderma or other connective tissue diseases (21%), or to autoimmune diseases (7%). There were no patients with pulmonary arterial hypertension associated with other conditions such as HIV disease or recurrent pulmonary emboli.

In both studies, Tracleer or placebo was added to patients' current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, and vasodilators (e.g., calcium channel blockers, ACE inhibitors), but not epoprostenol. Tracleer was given at a dose of 62.5 mg twice daily for 4 weeks and then at 125 mg twice daily or 250 mg twice daily for either 12 (BREATHE-1) or 8 (Study 351) additional weeks. The primary study endpoint was 6-minute walk distance. In addition, symptoms and functional status were assessed. Hemodynamic measurements were made at 12 weeks in Study 351.

The mean age was about 49 years. About 80% of patients were female, and about 80% were Caucasian. Patients had been diagnosed with pulmonary hypertension for a mean of 2.4 years.

#### Submaximal Exercise Ability

Results of the 6-minute walk distance at 3 months (Study 351) or 4 months (BREATHE-1) are shown in Table 3.

**Table 3. Effects of Tracleer on 6-minute walk distance**

	BREATHE-1			Study 351	
	Tracleer 125 mg twice daily (n = 74)	Tracleer 250 mg twice daily (n = 70)	Placebo (n = 69)	Tracleer 125 mg twice daily (n = 21)	Placebo (n = 11)
<b>Baseline</b>	326 ± 73	333 ± 75	344 ± 76	360 ± 86	355 ± 82
<b>End point</b>	353 ± 115	379 ± 101	336 ± 129	431 ± 66	350 ± 147
<b>Change from baseline</b>	27 ± 75	46 ± 62	-8 ± 96	70 ± 56	-6 ± 121
<b>Placebo – subtracted</b>	35 *	54 †		76 ‡	

Distance in meters: mean ± standard deviation. Changes are to week 16 for BREATHE-1 and to week 12 for Study 351.

\* p=0.01; by Wilcoxon;

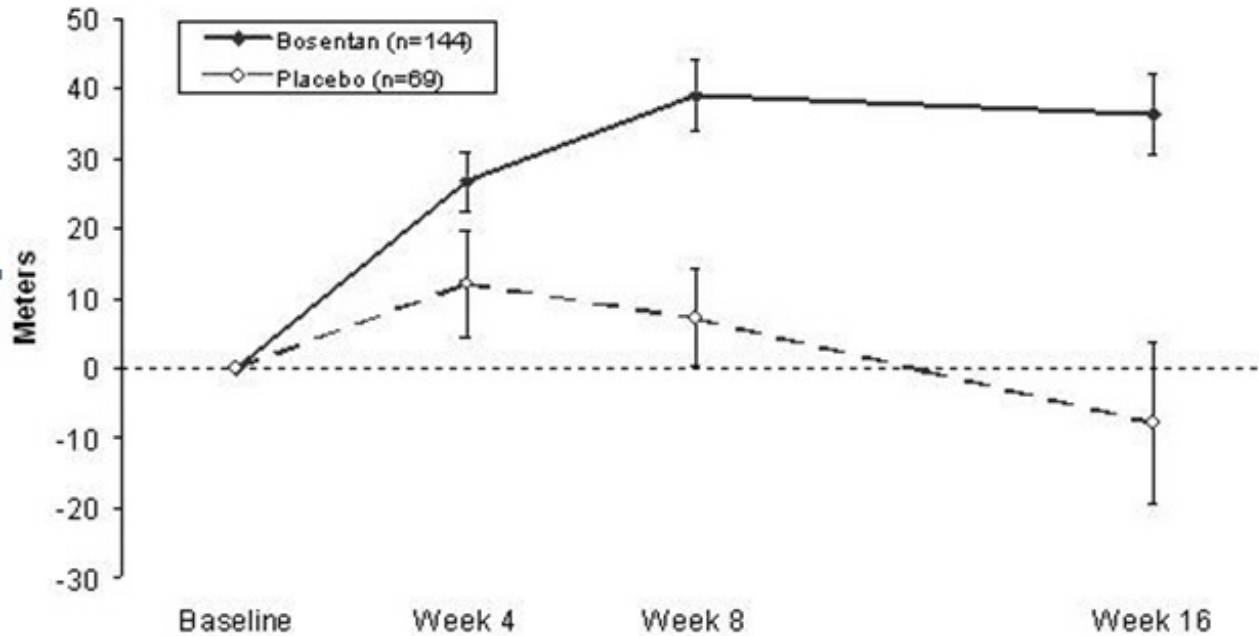
† p=0.0001; by Wilcoxon;

‡ p=0.02; by Student's t-test.

In both trials, treatment with Tracleer resulted in a significant increase in exercise ability. The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg twice daily) and fully developed by about 2 months of treatment (Figure 1). It was maintained for up to 7 months of

double-blind treatment. Walking distance was somewhat greater with 250 mg twice daily, but the potential for increased hepatotoxicity causes this dose not to be recommended [see *Dosage and Administration (2.1)*]. There were no apparent differences in treatment effects on walk distance among subgroups analyzed by demographic factors, baseline disease severity, or disease etiology, but the studies had little power to detect such differences.

Figure 1. Mean Change in 6-min Walk Distance (BREATHE-1)



**Change from baseline in 6-minute walking distance from start of therapy to week 16 in the placebo and combined Tracleer (125 mg twice daily and 250 mg twice daily) groups. Values are expressed as mean ± standard error of the mean.**

### Hemodynamic Changes

Invasive hemodynamic parameters were assessed in Study 351. Treatment with Tracleer led to a significant increase in cardiac index (CI) associated with a significant reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and mean right atrial pressure (RAP) (Table 4). The relationship between hemodynamic effects and improvements in 6-minute walk distance is unknown.

**Table 4: Change from Baseline to Week 12: Hemodynamic Parameters**

	<b>Tracleer 125 mg twice daily</b>	<b>Placebo</b>
<b>Mean CI (L/min/m<sup>2</sup>)</b>	n=20	n=10
Baseline	2.35±0.73	2.48±1.03
Absolute Change	0.50±0.46	-0.52±0.48
Treatment Effect		1.02*
<b>Mean PAP (mmHg)</b>	n=20	n=10
Baseline	53.7±13.4	55.7±10.5
Absolute Change	-1.6±5.1	5.1±8.8
Treatment Effect		-6.7†
<b>Mean PVR (dyn·sec·cm<sup>-5</sup>)</b>	n=19	n=10
Baseline	896±425	942±430
Absolute Change	-223±245	191±235

Treatment Effect		-415*
<b>Mean RAP (mmHg)</b>	n=19	n=10
Baseline	9.7±5.6	9.9±4.1
Absolute Change	-1.3±4.1	4.9±4.6
Treatment Effect		-6.2*

Values shown are means ± SD

\* p≤0.001;

† p<0.02

### **Symptoms and Functional Status**

Symptoms of pulmonary arterial hypertension were assessed by Borg dyspnea score, WHO functional class, and rate of "clinical worsening." Clinical worsening was assessed as the sum of death, hospitalizations for PAH, discontinuation of therapy because of PAH, and need for epoprostenol. There was a significant reduction in dyspnea during walk tests (Borg dyspnea score), and significant improvement in WHO functional class in Tracleer-treated patients. There was a significant reduction in the rate of clinical worsening (Table 5 and Figure 2). Figure 2 shows the log-rank test reflecting clinical worsening over 28 weeks.

**Table 5: Incidence of Clinical Worsening, Intent To Treat Population**

	<b>BREATHE-1</b>		<b>Study 351</b>	
	<b>Tracleer 125/250 mg twice daily (n = 144)</b>	<b>Placebo (n = 69)</b>	<b>Tracleer 125 mg twice daily (n = 21)</b>	<b>Placebo (n = 11)</b>
Patients with clinical worsening [n (%)]	9 (6%)*	14 (20%)	0 (0%)†	3 (27%)
Death	1 (1%)	2 (3%)	0 (0%)	0 (0%)
Hospitalization for PAH	6 (4%)	9 (13%)	0 (0%)	3 (27%)
Discontinuation due to worsening of PAH	5 (3%)	6 (9%)	0 (0%)	3 (27%)
Receipt of epoprostenol‡	4 (3%)	3 (4%)	0 (0%)	3 (27%)

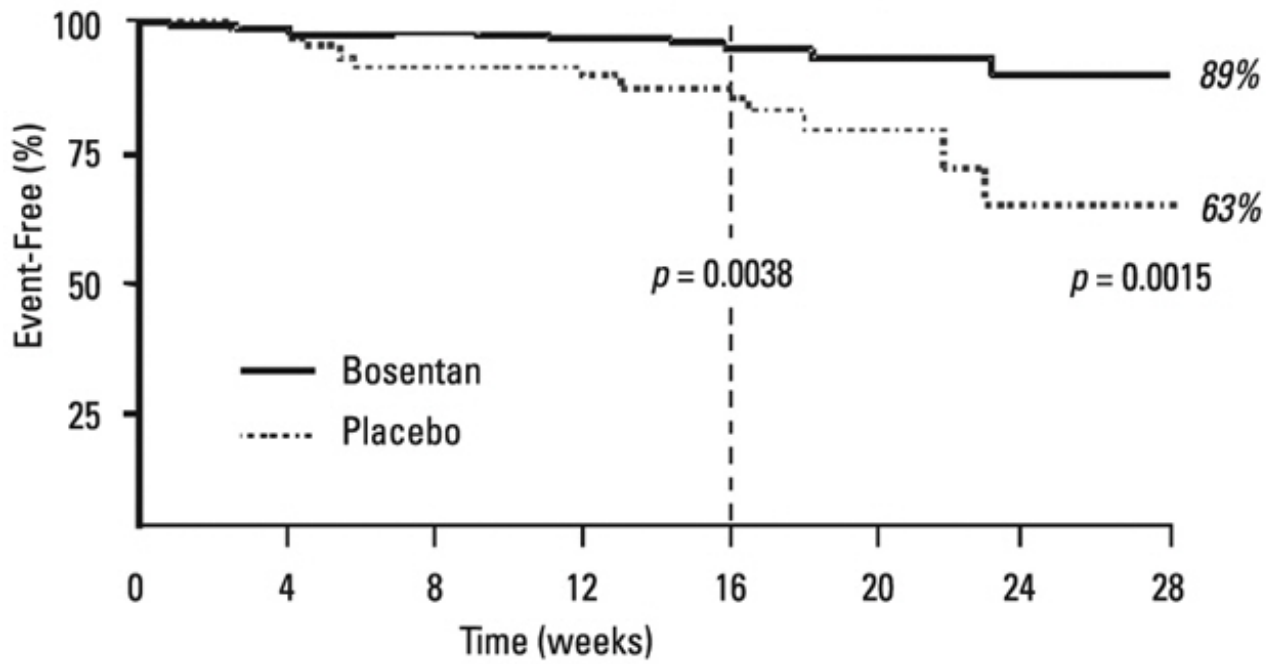
Note: Patients may have had more than one reason for clinical worsening.

\* p=0.0015 vs. placebo by log-rank test. There was no relevant difference between the 125 mg and 250 mg twice daily groups.

† p=0.033 vs. placebo by Fisher's exact test.

‡ Receipt of epoprostenol was always a consequence of clinical worsening.

**Figure 2. Time to Clinical Worsening (BREATHE-1)**



**Time from randomization to clinical worsening with Kaplan-Meier estimate of the proportions of failures in BREATHE-1. All patients (n=144 in the Tracleer group and n=69 in the placebo group) participated in the first 16 weeks of the study. A subset of this population (n=35 in the Tracleer group and 13 in the placebo group) continued double-blind therapy for up to 28 weeks.**

### **WHO Functional Class II**

In a randomized, double-blind, multicenter, placebo-controlled trial, 185 mildly symptomatic PAH patients with WHO Functional Class II (mean baseline 6-minute walk distance of 443 meters) received Tracleer 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily (n = 93), or placebo (n = 92) for 6 months. Enrolled patients were treatment-naïve (n = 156) or on a stable dose of sildenafil (n = 29). The coprimary endpoints were change from baseline to month 6 in PVR and 6-minute walk distance. Time to clinical worsening (assessed as the sum of death, hospitalization due to PAH complications, or symptomatic progression of PAH), Borg dyspnea index, change in WHO functional class and hemodynamics were assessed as secondary endpoints.

Compared with placebo, Tracleer treatment was associated with a reduced incidence of worsening of at least one functional class (3% Tracleer vs. 13% placebo,  $p = 0.03$ ), and improvement in hemodynamic variables (PVR, mPAP, TPR, cardiac index, and  $SVO_2$ ;  $p < 0.05$ ). The + 19 m mean (+14 m median) increase in 6-minute walk distance with Tracleer vs. placebo was not significant ( $p = 0.08$ ). There was a significant delay in time to clinical worsening (first seen primarily as symptomatic progression of PAH) with Tracleer compared with placebo (hazard ratio 0.2,  $p = 0.01$ ). Findings were consistent in strata with or without treatment with sildenafil at baseline.

### **Long-term Treatment of PAH**

Long-term follow-up of patients with Class III and IV PAH who were treated with Tracleer in open-label extensions of trials (N=235) showed that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment.

These uncontrolled observations do not allow comparison with a group not given Tracleer and cannot be used to determine the long-term effect of Tracleer on mortality.

### **Pulmonary Arterial Hypertension related to Congenital Heart Disease with Left-to-Right Shunts**

A small study (N=54) and its open label extension (N=37) of up to 40 weeks with patients with Eisenmenger physiology demonstrated effects of Tracleer on exercise and safety that were similar to

those seen in other trials in patients with PAH (WHO Group 1).

## **14.2 Lack of Benefit in Congestive Heart Failure**

Tracleer is not effective in the treatment of congestive heart failure with left ventricular dysfunction. In a pair of studies, 1613 subjects with NYHA Class III-IV heart failure, left ventricular ejection fraction <35%, on diuretics, ACE inhibitor, and other therapies, were randomized to placebo or Tracleer (62.5 mg twice daily titrated as tolerated to 125 mg twice daily) and followed for up to 70 weeks. Use of Tracleer was associated with no benefit on patient global assessment (the primary end point) or mortality. However, hospitalizations for heart failure were more common during the first 4 to 8 weeks after Tracleer was initiated. In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

## **16. HOW SUPPLIED/STORAGE AND HANDLING**

62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62,5", packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap or in foil blister-strips for hospital unit-dosing.

NDC 66215-101-06: Bottle containing 60 tablets.

NDC 66215-101-03: Carton of 30 tablets in 10 blister strips of 3 tablets.

125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125", packaged in a white high-density polyethylene bottle and a white polypropylene child-resistant cap or in foil blister-strips for hospital unit-dosing.

NDC 66215-102-06: Bottle containing 60 tablets.

NDC 66215-102-03: Carton of 30 tablets in 10 blister strips of 3 tablets.

Store at 20°C – 25°C (68°F – 77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature].

Manufactured for:

Actelion Pharmaceuticals US, Inc.

South San Francisco, CA 94080, USA

ACT20160901

## **17. PATIENT COUNSELING INFORMATION**

**See FDA-approved patient labeling (Medication Guide)**

### **Restricted access**

Advise the patient that Tracleer is only available through a restricted access program called the Tracleer REMS Program.

As a component of the Tracleer REMS, prescribers must review the contents of the Tracleer Medication Guide with the patient before initiating Tracleer.

Instruct patients that the risks associated with Tracleer include:

- **Hepatotoxicity**  
Discuss with the patient the requirement to measure serum aminotransferases monthly.
- **Embryo-fetal toxicity**  
Educate and counsel female patients of reproductive potential about the need to use reliable methods

of contraception during treatment with Tracleer and for one month after treatment discontinuation. Females of reproductive potential must have monthly pregnancy tests and must use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer [see *Use in Specific Populations (8.1)*].

Females who have intrauterine devices (IUD) or tubal sterilization can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant. Patients should seek additional contraceptive advice from a gynecologist or similar expert as needed.

Educate and counsel females of reproductive potential on the use of emergency contraception in the event of unprotected sex or contraceptive failure.

Advise pre-pubertal females to report any changes in their reproductive status immediately to her prescriber.

Advise patients to contact their gynecologist or healthcare provider if they want to change the form of birth control which is used to ensure that another acceptable form of birth control is selected.

Advise the patient that Tracleer is available only from specialty pharmacies that are enrolled in Tracleer REMS Program.

Patients must sign the Tracleer Patient Enrollment and Consent Form to confirm that they understand the risks of Tracleer.

### **Other Risks Associated with Tracleer**

Instruct patients that the risks associated with Tracleer also include the following:

Decreases in hemoglobin and hematocrit – advise patients of the importance of hemoglobin testing

Decreases in sperm count

Fluid retention

### **Medication Guide**

#### **Tracleer® (tra-KLEER)**

#### **(bosentan)**

#### **Tablets**

Read the Medication Guide that comes with Tracleer before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking with your healthcare provider about your medical condition or your treatment.

#### **What is the most important information I should know about Tracleer?**

Tracleer is only available through the Tracleer REMS Program. Before you begin taking Tracleer, you must read and agree to all of the instructions in the Tracleer REMS Program.

#### **Tracleer can cause serious side effects including:**

##### **Liver damage.**

- Liver damage may not cause symptoms at first. Only a blood test can show if you have early liver damage. You must have your blood tested to check your liver function before you start Tracleer and each month after that. Your healthcare provider will order these tests. Regular blood tests are important because they will help your healthcare provider adjust or stop your treatment before there is permanent damage.
- Tell your healthcare provider if you have had liver problems, including liver problems while taking other medicines. Call your healthcare provider right away if you have any of these symptoms of liver problems while taking Tracleer:
  - nausea
  - vomiting
  - fever

- unusual tiredness
- stomach area (abdominal) pain
- yellowing of the skin or the whites of your eyes (jaundice)

### **Serious birth defects.**

- **Tracleer can cause serious birth defects if taken during pregnancy. You must not be pregnant when you start taking Tracleer or during Tracleer treatment. Serious birth defects from Tracleer can happen early in pregnancy. Females who are able to get pregnant must have a negative pregnancy test before starting treatment with Tracleer each month during treatment with Tracleer and 1 month after stopping treatment with Tracleer.**
  - Talk to your healthcare provider about your menstrual cycle. Your healthcare provider will decide when to do a pregnancy test and will order a pregnancy test for you depending on your menstrual cycle.
    - Females who **are able** to get pregnant are females who:
      - have entered puberty, even if they have not started their menstrual period, **and**
      - have a uterus, **and**
      - have not gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed.
    - Females who **are not able** to get pregnant are females who:
      - have not yet entered puberty, **or**
      - do not have a uterus, **or**
      - have gone through menopause. Menopause means that you have not had a menstrual period for at least 12 months for natural reasons, or that you have had your ovaries removed **or**
      - are infertile for other medical reasons and this infertility is permanent and cannot be reversed.
- **Females who are able to get pregnant must use two acceptable forms of birth control during treatment with Tracleer, and for one month after stopping Tracleer because the medicine may still be in the body.**
  - If you have had a tubal sterilization or have an IUD (intrauterine device), these methods can be used alone and no other form of birth control is needed.
  - Talk with your healthcare provider or gynecologist (a doctor who specializes in female reproduction) to find out about options for acceptable birth control that you may use to prevent pregnancy during treatment with Tracleer.
  - If you decide that you want to change the form of birth control that you use, talk with your healthcare provider or gynecologist to be sure that you choose another acceptable form of birth control.

### **See the chart below for Acceptable Birth Control Options during treatment with Tracleer.**

- **Do not have unprotected sex. Talk to your healthcare provider or pharmacist right away if you have unprotected sex or if you think your birth control has failed. Your healthcare provider may talk with you about using emergency birth control.**
- **Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.**

If you are the parent or caregiver of a female child who started taking Tracleer before reaching puberty, you should check your child regularly to see if she is developing signs of puberty. Tell your healthcare provider right away if you notice that she is developing breast buds or any pubic hair. Your healthcare provider should decide if your child has reached puberty. **Your child may reach puberty before having her first menstrual period.**

## Acceptable birth control options

Option 1	or	Option 2	or	Option 3	or	Option 4
One method from this list:		One method from this list:		One method from this list:		One method from this list:
Standard intrauterine device (Copper T 380A IUD) Intrauterine system (LNg 20 IUS: progesterone IUS) Tubal sterilization		Estrogen and progesterone oral contraceptives ("the pill") Estrogen and progesterone transdermal patch Vaginal ring Progesterone injection Progesterone implant		Diaphragm with spermicide Cervical cap with spermicide		Partner's vasectomy
		PLUS One method from this list:		PLUS One method from this list:		PLUS One method from this list:
		Male condom Diaphragm with spermicide Cervical cap with spermicide		Male condom		Male condom Diaphragm with spermicide Cervical cap with spermicide Estrogen and progesterone oral contraceptives ("the pill") Estrogen and progesterone transdermal patch Vaginal ring Progesterone injection Progesterone implant

See "**What are the possible side effects of Tracleer?**" for more information about side effects.

### What is Tracleer?

Tracleer is a prescription medicine used to treat people with certain types of pulmonary arterial hypertension (PAH), which is high blood pressure in the vessels of the lungs.

Tracleer can improve your ability to exercise and can slow the worsening of your physical condition and symptoms. Tracleer lowers high blood pressure in your lungs and lets your heart pump blood more efficiently.

### Tracleer is only:

Prescribed by healthcare providers who are enrolled in the Tracleer REMS Program.

Available to people who understand and agree to enroll in the Tracleer REMS Program.

It is not known if Tracleer is safe and works in children below 12 years of age.

### Who should not take Tracleer?

#### Do not take Tracleer if you:

- **are pregnant, plan to become pregnant, or become pregnant during Tracleer treatment.**  
Tracleer can cause serious birth defects. All females should read the **birth defects** section of



## "What is the most important information I should know about Tracleer?"

- take any of these medicines:
  - cyclosporine A used to treat psoriasis and rheumatoid arthritis, and to prevent rejection of heart, liver, and kidney transplants
  - glyburide used to treat diabetes
- are allergic to bosentan or any of the ingredients in Tracleer. See the end of this Medication Guide for a complete list of the ingredients in Tracleer. If you have a rash, hives or your lips swell after taking Tracleer, it may be a sign of allergy. You should stop taking your Tracleer and talk to your healthcare provider.

## What should I tell my healthcare provider before taking Tracleer?

Tracleer may not be right for you. **Tell your healthcare provider about all your medical conditions, including if you:**

- **have liver problems.**
- **are breast-feeding or plan to breast feed.** It is not known if Tracleer passes into your milk. You and your healthcare provider should decide if you will take Tracleer or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Tracleer and other medicines may affect how each other works and cause side effects. Especially tell your healthcare provider if you take:

- hormone-based birth control, such as pills, shots, patches, and implants. These birth control methods may not work as well when taken with Tracleer.
- simvastatin or other "-statin" medicines used to lower cholesterol
- rifampin used for tuberculosis
- tacrolimus used to prevent rejection of liver or kidney transplant
- ketoconazole, fluconazole, itraconazole, or voriconazole used for fungal infections
- warfarin sodium used to prevent blood clots
- ritonavir used to treat HIV

There may be more than one brand name medicine. Ask your healthcare provider if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of them and show it to your healthcare provider or pharmacist when you get a new medicine.

## How should I take Tracleer?

Your healthcare provider will give you detailed information about the Tracleer REMS Program.

- Tracleer will be mailed to you by a specialty pharmacy. You will only receive a 30-day supply of Tracleer at one time.
- Take Tracleer exactly as prescribed.
- Your healthcare provider will tell you how much Tracleer to take and when to take it.
- In most cases, you will take 1 tablet in the morning and 1 in the evening.
- You can take Tracleer with or without food.
- If you take more than the prescribed dose of Tracleer, call your healthcare provider right away.
- If you miss a dose of Tracleer, take your tablet as soon as you remember. Do not take 2 doses at the same time. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time.
- Do not stop taking Tracleer unless your healthcare provider tells you to. Suddenly stopping your treatment may cause your symptoms to get worse. If you need to stop taking Tracleer, speak with your healthcare provider about the right way to stop.

## What are the possible side effects of Tracleer?

Tracleer can cause serious side effects, including:

- **See "What is the most important information I should know about Tracleer?"**
- **Fluid retention and swelling of your ankles and legs.** Tracleer can cause your body to hold too much water, and you may get swelling of your ankles and legs. Tell your healthcare provider if you have swelling of your ankles and legs that happens either with or without weight gain, or if you have more trouble with your breathing than normal. Your healthcare provider will look for the cause of this.
- **Lower Sperm Count.** Some men who take Tracleer may have lower sperm counts. This may affect your ability to father a child. Tell your healthcare provider if fertility is a concern for you.
- **Low red blood cell levels (anemia).** Your healthcare provider will do blood tests to check your red blood cells during treatment with Tracleer.

### The most common side effects of Tracleer include:

- respiratory tract infection
- headache
- fainting
- flushing
- low blood pressure
- inflamed nose passages (sinusitis)
- joint pain
- irregular heart beats

Tell your doctor if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of Tracleer. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### How should I store Tracleer?

- Store Tracleer at room temperature between 68°F to 77°F (20°C to 25°C).

### Keep Tracleer and all medicines out of the reach of children.

### General information about Tracleer

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use Tracleer for a condition for which it was not prescribed. Do not give Tracleer to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about Tracleer. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about Tracleer that is written for health professionals. For more information, go to [www.Tracleer.com](http://www.Tracleer.com) or call 1-866-228-3546.

### What are the ingredients in Tracleer?

Active ingredient: bosentan

Inactive ingredients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, ethylcellulose.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:

Actelion Pharmaceuticals US, Inc.  
South San Francisco, CA 94080, USA

ACT20160901  
Revised: October 2016

**PRINCIPAL DISPLAY PANEL - 62.5 mg Tablet Bottle Carton**

NDC 66215-101-06

**Tracleer®**  
BOSENTAN  
**62.5 mg**

Rx only  
**ACTELION**

**60** tablets



**PRINCIPAL DISPLAY PANEL - 125 mg Tablet Bottle Carton**

NDC 66215-102-06

**Tracleer®**  
**BOSENTAN**  
**125 mg**

Rx only  
**ACTELION**

60 tablets



## TRACLEER

bosentan tablet, film coated

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:66215-101
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
bosentan (UNII: Q326023R30) (bosentan anhydrous - UNII:XUL93R30K2)	bosentan anhydrous	62.5 mg

### Inactive Ingredients

Ingredient Name	Strength
starch, corn (UNII: O8232NY3SJ)	
sodium starch glycolate type a potato (UNII: 5856J3G2A2)	
povidone k90 (UNII: RDH86HJV5Z)	
glyceryl dibehenate (UNII: R8WTH25YS2)	
magnesium stearate (UNII: 70097M6B0)	
hypromellose, unspecified (UNII: 3NXW29V3WO)	
triacetin (UNII: XHX3C3X673)	
talc (UNII: 7SEV7J4RIU)	
titanium dioxide (UNII: 15FIX9V2JP)	
ferric oxide yellow (UNII: EX438O2MRT)	
ferric oxide red (UNII: 1K09F3G675)	
ethylcellulose, unspecified (UNII: 7Z8S9VYZ4B)	

### Product Characteristics

<b>Color</b>	WHITE (orange-white)	<b>Score</b>	no score
<b>Shape</b>	ROUND	<b>Size</b>	6 mm
<b>Flavor</b>		<b>Imprint Code</b>	62;5
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:66215-101-06	1 in 1 CARTON	11/20/2001	
1		60 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product		
2	NDC:66215-101-03	10 in 1 CARTON	10/02/2012	
2		3 in 1 BLISTER PACK; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021290	11/20/2001	

# TRACLEER

bosentan tablet, film coated

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:66215-102
<b>Route of Administration</b>	ORAL		

## Active Ingredient/Active Moiety

<b>Ingredient Name</b>	<b>Basis of Strength</b>	<b>Strength</b>
<b>bosentan</b> (UNII: Q326023R30) (bosentan anhydrous - UNII:XUL93R30K2)	bosentan anhydrous	125 mg

## Inactive Ingredients

<b>Ingredient Name</b>	<b>Strength</b>
<b>starch, corn</b> (UNII: O8232NY3SJ)	
<b>sodium starch glycolate type a potato</b> (UNII: 5856J3G2A2)	
<b>povidone k90</b> (UNII: RDH86HJV5Z)	
<b>glyceryl dibehenate</b> (UNII: R8WTH25YS2)	
<b>magnesium stearate</b> (UNII: 70097M6B30)	
<b>hypromellose, unspecified</b> (UNII: 3NXW29V3WO)	
<b>triacetin</b> (UNII: XHX3C3X673)	
<b>talc</b> (UNII: 7SEV7J4R1U)	
<b>titanium dioxide</b> (UNII: 15FIX9V2JP)	
<b>ferric oxide yellow</b> (UNII: EX438O2MRT)	
<b>ferric oxide red</b> (UNII: 1K09F3G675)	
<b>ethylcellulose, unspecified</b> (UNII: 7Z8S9VYZ4B)	

## Product Characteristics

<b>Color</b>	WHITE (orange-white)	<b>Score</b>	no score
<b>Shape</b>	OVAL	<b>Size</b>	11mm
<b>Flavor</b>		<b>Imprint Code</b>	125
<b>Contains</b>			

## Packaging

<b>#</b>	<b>Item Code</b>	<b>Package Description</b>	<b>Marketing Start Date</b>	<b>Marketing End Date</b>
1	NDC:66215-102-06	1 in 1 CARTON	11/20/2001	
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## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA021290	11/20/2001	

**Labeler** - Actelion Pharmaceuticals US, Inc. (002641228)

Revised: 11/2016

Actelion Pharmaceuticals US, Inc.