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
TRACLEER® (bosentan) tablets for oral suspension
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 (5.3): 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 (2.1, 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 (2.4, 5.1).**

Based on animal data, Tracleer is likely to cause major birth defects if used during pregnancy (4.1, 5.2, 8.1).

- **Must exclude pregnancy before and during treatment (2.1, 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, 5.2, 8.1).**

---------- INDICATIONS AND USAGE----------

Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO 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).
- in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability. (1)

----------DOSAGE AND ADMINISTRATION----------

- Patients older than 12 years of age: initiate at 62.5 mg orally twice daily; for patients weighing greater than 40 kg, increase to 125 mg orally twice daily after 4 weeks (2.2).
- Patients 12 years of age and younger: dosage is is based on weight, see Table 1 (2.2).
- Reduce the dose and closely monitor patients developing aminotransferase elevations more than 3 X Upper Limit of Normal (ULN) (2.1).

---------- DOSAGE FORMS AND STRENGTHS ----------

- Film-coated tablet: 62.5 mg and 125 mg (3)
- Tablet for oral suspension: 32 mg (3)

---------- CONTRAINDICATIONS ----------

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

---------- WARNINGS AND PRECAUTIONS ----------

- 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) for the film-coated tablet are respiratory tract infection and anemia (6.1).
- Common adverse reactions (≥15%) for the dispersible tablet are upper respiratory tract infections and pyrexia (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----------

- Cytochrome P450: Coadministration of Tracleer with drugs metabolized by CYP2C9 and CYP3A can increase exposure to Tracleer and/or the coadministered drug (4.2, 4.3, 7.1)
- Hormonal contraceptives: Tracleer use decreases contraceptive exposure and reduces effectiveness (7.2).

---------- USE IN SPECIFIC POPULATIONS ----------

- Nursing mothers: Choose breastfeeding or Tracleer (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

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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 (5.3)]*.

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 (2.4), 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 (2.4)]*.

Elevations in aminotransferases require close attention *[see Dosage and Administration (2.4)]*. 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 Warnings and Precautions (5.2), 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

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

- in adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO 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)]*.
- in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

2. DOSAGE AND ADMINISTRATION

2.1 Required Monitoring

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 (5.3)]*.

Obtain a pregnancy test in females of reproductive potential prior to Tracleer treatment, monthly during treatment and one month after stopping Tracleer. Initiate treatment with Tracleer in females of reproductive potential only after a negative pregnancy test *[see Boxed Warning, Contraindications (4.1), Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

Measure liver aminotransferase levels prior to initiation of treatment and then monthly *[see Warnings and Precautions (5.1)]*.

2.2 Recommended Dosage

Administer Tracleer orally following the dosing recommendations in Table 1. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of hepatotoxicity.

Table 1: Dosing Recommendations

	Initial 4 weeks	Maintenance (after 4 weeks)
Patients >12 years of age and >40 kg	62.5 mg twice daily	125 mg twice daily
Patients >12 years of age and <40 kg	62.5 mg twice daily	62.5 mg twice daily

Patients ≤12 years of age		
≥4-8 kg	16 mg twice daily	16 mg twice daily
>8-16 kg	32 mg twice daily	32 mg twice daily
>16-24 kg	48 mg twice daily	48 mg twice daily
>24-40 kg	64 mg twice daily	64 mg twice daily

2.3 Administration

Tracleer film-coated tablets and tablets for oral suspension (dispersible tablets) should be administered orally twice daily.

Disperse tablets for oral suspension, or dispersible tablet half, in a minimal amount of water immediately before administration.

Store divided dispersible tablet pieces at 20ºC – 25ºC (68ºF – 77ºF) in the opened blister for up to 7 days.

2.4 Dosage Adjustments for Aminotransferase Elevations

If aminotransferase levels increase, adjust monitoring and treatment plan according to Table 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 bilirubin ≥ 2 x Upper Limit of Normal (ULN). There is no experience with the reintroduction of Tracleer in these circumstances.

Table 2: 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, - in adults and pediatric patients >12 years and >40 kg, 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, treatment may continue or be reintroduced at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. - in all other pediatric patients, interrupt treatment with no prior dose reduction. If the aminotransferase levels return to pretreatment values, reintroduce at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
> 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, - in adults and pediatric patients >12 years and >40 kg, consider reintroduction of treatment at 62.5 mg twice daily, with reassessment of aminotransferase levels within 3 days. - in all other pediatric patients, consider reintroduction at the dose used prior to treatment interruption, with reassessment of aminotransferase levels within 3 days.
> 8 x ULN	Stop treatment permanently. There is no experience with reintroduction of Tracleer in these circumstances.

2.5 Use with Ritonavir

Co-administration of Tracleer in Patients on Ritonavir
In patients who have been receiving ritonavir for at least 10 days, start Tracleer at the recommended initial dose once daily or every other day based upon individual tolerability *[see Cytochrome P450 Drug Interactions (7.1)]*.

Co-administration 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 the recommended initial dose once daily or every other day based upon individual tolerability *[see Cytochrome P450 Drug Interactions (7.1)]*.

2.6 Use in Patients with Pre-existing Hepatic Impairment

Avoid initiation of Tracleer in patients with 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)]*.

3. DOSAGE FORMS AND STRENGTHS

62.5 mg tablets: round, biconvex, orange-white tablets, debossed with identification marking "62,5"

125 mg tablets: oval, biconvex, orange-white tablets, debossed with identification marking "125"

32 mg tablets for oral suspension: clover-shaped, quadrisected, pale yellow to off-white tablets, debossed with identification marking "32" on the side opposite the quadrisection lines

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

Co-administration of cyclosporine A and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of Tracleer and cyclosporine A is contraindicated *[see Cytochrome P450 Drug Interactions (7.1)]*.

4.3 Use with Glyburide

An increased risk of liver enzyme elevations was observed in patients receiving glyburide concomitantly with bosentan. Therefore co-administration of glyburide and Tracleer is contraindicated *[see Cytochrome P450 Drug Interactions (7.1)]*.

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

ALT or AST > 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 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 ≥ 3 x ULN were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with Tracleer. In a pooled analysis of four pediatric studies conducted in PAH (n =100), elevations in liver aminotransferases ≥ 3 × ULN were observed in 2% of patients. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 2 x 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 (2.1, 2.4)]*. 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.

Avoid initiation of Tracleer in patients with elevated aminotransferases (> 3 x ULN) prior to drug initiation because monitoring hepatotoxicity in these patients may be more difficult *[see Boxed Warning, Dosage and Administration (2.6), Use in Specific Populations (8.6)]*.

In WHO Functional Class II patients, consider whether the benefits of Tracleer are sufficient to offset the risk of hepatotoxicity, which may preclude future use as their disease progresses.

5.2 Embryo-fetal Toxicity

Based on data from animal reproduction studies, Tracleer may cause fetal harm when administered to a pregnant female and is contraindicated in females who are pregnant. Advise females of reproductive potential of the potential risk to a fetus. Obtain a pregnancy test prior to Tracleer treatment, monthly during treatment and for one month after stopping treatment. Advise females of reproductive potential to use two reliable forms of contraception during treatment with Tracleer and for at least one month after the last dose *[see Dosage and Administration (2), Use in Specific Populations (8.1, 8.3)]*.

Tracleer is only available for females through a restricted program under REMS *[see Warnings and Precautions (5.3)]*.

5.3 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, Warnings and Precautions (5.1, 5.2), 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.Tracleerrems.com or 1-866-228-3546.

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% (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), Clinical Studies (14.2)]*.

5.5 Pulmonary Veno-Occlusive Disease

If 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, similar to 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)]*
- Embryo-fetal Toxicity *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Fluid Retention *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials 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 adult patients with PAH 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 PAH 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 adult patients with PAH 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 PAH at doses of 125 or 250 mg twice daily are shown in Table 3:

Table 3. 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

Adverse Event	Tracleer n = 258		Placebo n = 172	
	No.	**%**	**No.**	**%**
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%	-	-

*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.

** Respiratory Tract Infection combines the terms "Nasopharyngitis", "Upper Respiratory Tract Infection" and "Respiratory Tract Infection". Combined data from Study 351, BREATHE-1 and EARLY

Tracleer was evaluated for safety in 119 pediatric patients in uncontrolled studies. The safety profile was similar to that observed in adult patients with PAH.

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 adult 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.

In a pooled analysis of pediatric patients (N=100) with PAH treated with Tracleer, a decrease in hemoglobin levels to < 10 g/dL from baseline was reported in 11% of patients. There was no decrease to < 8 g/dL.

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 Drug Interactions

Bosentan is metabolized by CYP2C9 and CYP3A. Inhibition of these enzymes may increase the plasma concentration of bosentan *[see Pharmacokinetics (12.3)]*. 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. Co-administration 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 co-administered. 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.

Figure 1. CYP3A induction-mediated effect of bosentan on other drugs

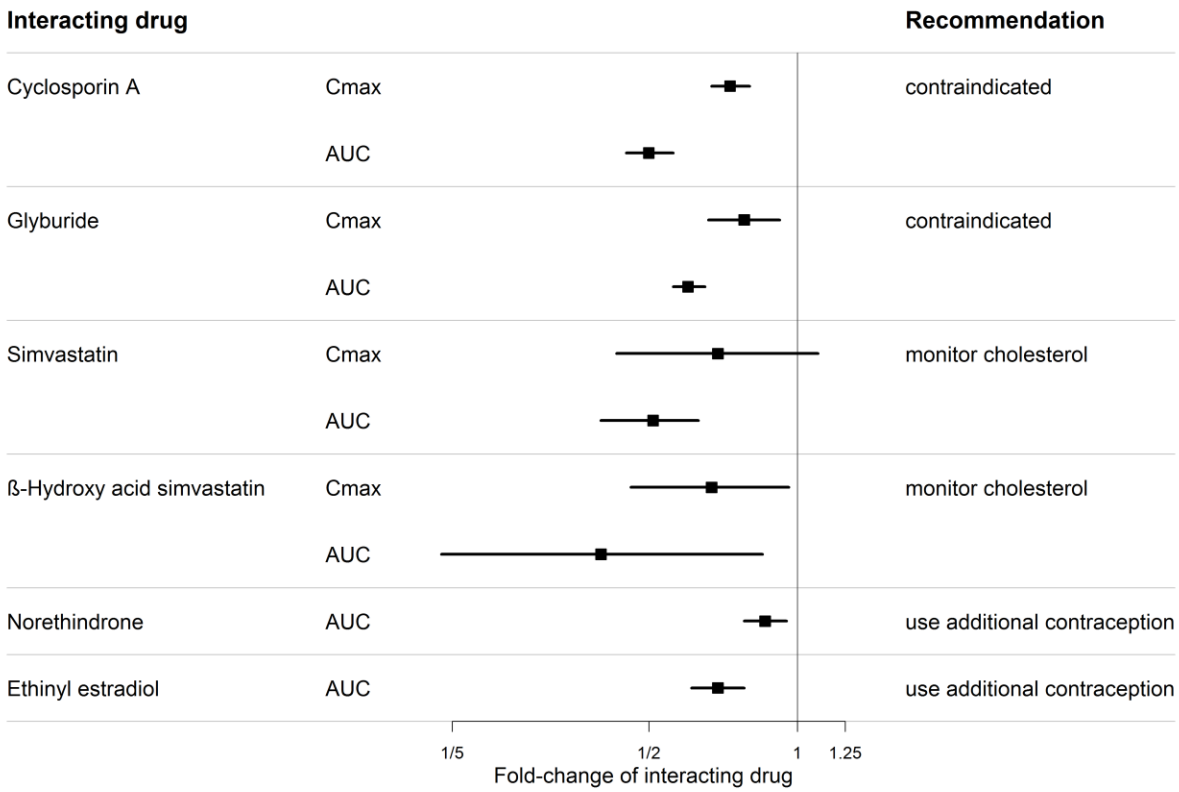
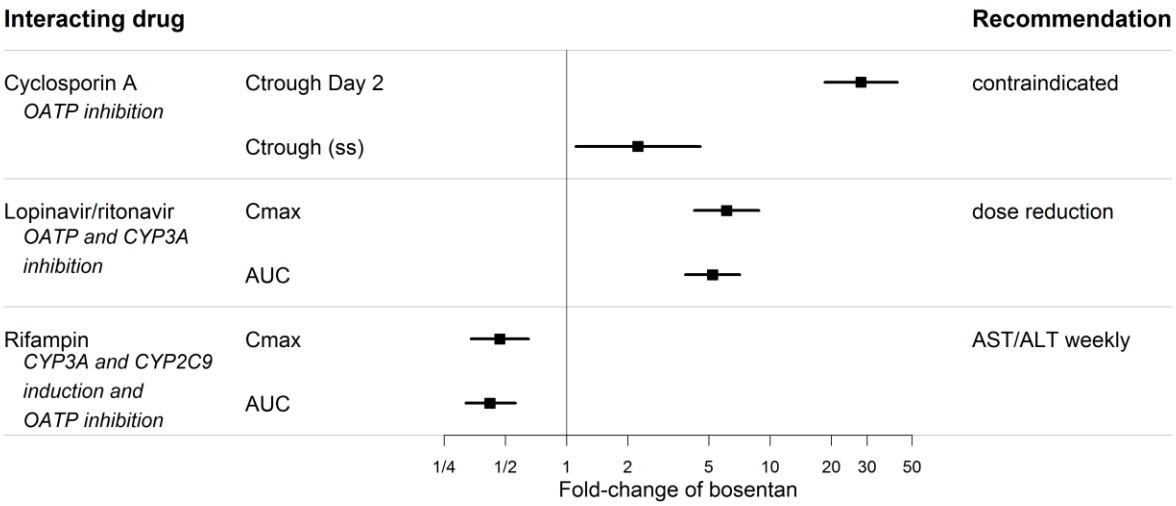


Figure 2. Effect of other drugs on bosentan



7.2 Hormonal Contraceptives

Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when Tracleer is co-administered. Females should practice additional methods of contraception and not rely on hormonal contraception alone when taking Tracleer *[see Use in Specific Populations (8.3)]*.

An interaction study demonstrated that co-administration 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.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on data from animal reproduction studies, Tracleer may cause fetal harm, including birth defects and fetal death, when administered to a pregnant female and is contraindicated during pregnancy *[see Contraindications (4.1)]*. There are limited data on Tracleer use in pregnant women. In animal reproduction studies, oral administration of bosentan to pregnant rats at 2-times the maximum recommended human dose (MRHD) on a mg/m^2 basis caused teratogenic effects in rats, including malformations of the head, mouth, face, and large blood vessels [*see Animal Data*]. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Bosentan was teratogenic in rats given oral doses two times the MRHD (on a mg/m^2 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^2 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.

8.2 Lactation

Risk Summary

There are no data on the presence of bosentan in human milk, the effects on the breastfed infant, or the effect on milk production. Because of the potential for serious adverse reactions, such as fluid retention and hepatotoxicity, in breastfed infants from Tracleer, advise women not to breastfeed during treatment with Tracleer.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Tracleer, monthly during treatment and one month after stopping treatment with 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 two acceptable methods of contraception during treatment 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]*.

Infertility

Males

Decreased sperm counts have been observed in patients receiving Tracleer. Based on these findings and findings in animals, Tracleer may impair fertility in males of reproductive potential.

It is not known whether effects on fertility would be reversible *[see Warnings and Precautions (5.6), Adverse Reactions (6.1), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The efficacy of Tracleer in patients <18 years is supported by data from an uncontrolled trial in which 19 pediatric patients were treated with Tracleer. In this study, cardiopulmonary hemodynamic improvements were similar to those seen in adults treated with Tracleer *[see Pulmonary Arterial Hypertension (14.1)]*. Safety in pediatric patients is supported by data from 100 pediatric patients treated with Tracleer for a median of 17 months *[see Clinical Studies Experience (6.1), Pulmonary Arterial Hypertension (14.1)]*.

Juvenile Animal Toxicity Data

In a juvenile rat toxicity study, rats were treated from Day 4 postpartum to adulthood (Day 69 postpartum). Decreased body weights, absolute weights of testes and epididymides, and reduced number of sperm in epididymides were observed after weaning. No effect on testis histology or sperm morphology and function was seen. The NOAEL was 4 times (at Day 4 postpartum) and 2 times (Day 69 postpartum) the human therapeutic exposure, respectively.

No effects on general development, sensory, cognitive function and reproductive performance were detected at the highest dose tested in juvenile rats, 7 times the therapeutic exposure in children with PAH.

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 have 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 were not altered in patients with mild impairment of hepatic function (Child-Pugh Class A) *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), 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

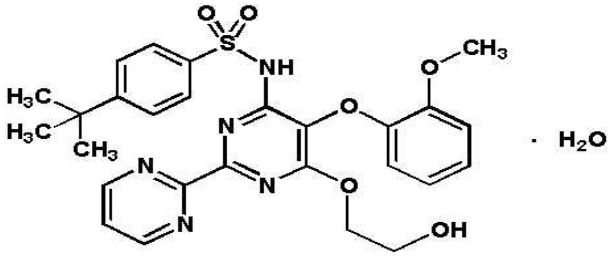
cyclosporine A, trough plasma concentrations of bosentan increased 30-fold, resulting in severe headache, nausea, and vomiting, but no serious adverse events. Mild decreases in blood pressure and increases in heart rate were observed.

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 $C_{27}H_{29}N_5O_6S{\bullet}H_2O$. 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 64.54 mg of bosentan monohydrate, equivalent to 62.5 mg of anhydrous bosentan. Each Tracleer 125 mg tablet contains 129.08 mg of bosentan monohydrate, equivalent to 125 mg of anhydrous bosentan.

Tracleer is also available as a 32 mg tablet for oral suspension and contains the following excipients: cellulose microcrystalline, calcium hydrogen phosphate anhydrous, croscarmellose sodium, silica colloidal anhydrous, tartaric acid, tutti frutti flavor, aspartame (E951), acesulfame potassium, and magnesium stearate. Each dispersible tablet contains 1.87 mg of phenylalanine. Each dispersible tablet contains 33.045 mg of bosentan monohydrate, equivalent to 32 mg anhydrous bosentan.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B 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_A and ET_B receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with PAH, 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 is about 5 hours in healthy adult subjects. The exposure to bosentan after intravenous and oral administration is about twice as high in adult patients with PAH as it is in healthy adult subjects.

In a relative bioavailability study in healthy adults, the peak plasma concentration and area under the plasma concentration-time curve for bosentan are on an average 14% and 11%, respectively, lower following administration of the oral dispersible tablet compared to the film-coated tablet.

Absorption

The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food.

Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes. The volume of distribution is about 18 L.

Elimination

Metabolism

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. 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.

Excretion

Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine. Total clearance after a single intravenous dose is about 4 L/h in patients with PAH.

Specific Populations

Pediatrics

The average plasma exposure to bosentan at steady state (AUC_{ss}) in pediatric patients with PAH aged 3 to 15 years treated with 31.25, 62.5 or 125 mg (approximately 2 mg/kg) film-coated tablet

twice daily is 37% lower than that observed in adult patients with PAH receiving 125 mg film-coated tablet twice daily. Following administration of 4 mg/kg twice daily doses of dispersible tablet in patients with PAH aged 2 to 11 years, the average systemic exposure to bosentan at steady state is similar to that observed with 2 mg/kg. The average exposure to bosentan in these pediatric patients was approximately half the exposure in adult patients treated with 125 mg film-coated tablets twice daily.

The exposure to bosentan at 2 mg/kg three times daily dosing of dispersible tablet is similar to that of 2 mg/kg twice daily dosing in patients with PAH aged 3 months to 12 years.

Based on these findings, exposure to bosentan reaches a plateau at lower doses in pediatric patients than in adults, and doses higher than 2 mg/kg twice daily do not increase the exposure to bosentan in pediatric patients.

Hepatic Impairment

In vitro and *in vivo* evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment could significantly increase exposure to 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 were 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 PAH associated with portal hypertension than in 3 patients with normal liver function and PAH of other etiologies.

The pharmacokinetics of Tracleer have not been evaluated in patients with severe liver impairment (Child-Pugh Class C) *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), 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 subjects with normal renal function. These differences do not appear to be clinically important.

Drug Interactions

Ketoconazole

Co-administration of bosentan 125 mg twice daily and ketoconazole, a potent CYP3A inhibitor, increased the plasma concentrations of bosentan by approximately 100% in normal volunteers. No dose adjustment of Tracleer is necessary, but increased effects of Tracleer should be considered.

Warfarin

Co-administration 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 PAH 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.

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.

Sildenafil

In normal volunteers, co-administration 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 PAH or erectile dysfunction.

Tadalafil

Bosentan (125 mg twice daily) reduced tadalafil (40 mg once per day) systemic exposure (AUC) by 42% and Cmax by 27% following multiple dose co-administration. Tadalafil did not affect the exposure (AUC and Cmax) of bosentan or its metabolites.

Figure 3. CYP Induction-mediated effect of bosentan on other drugs

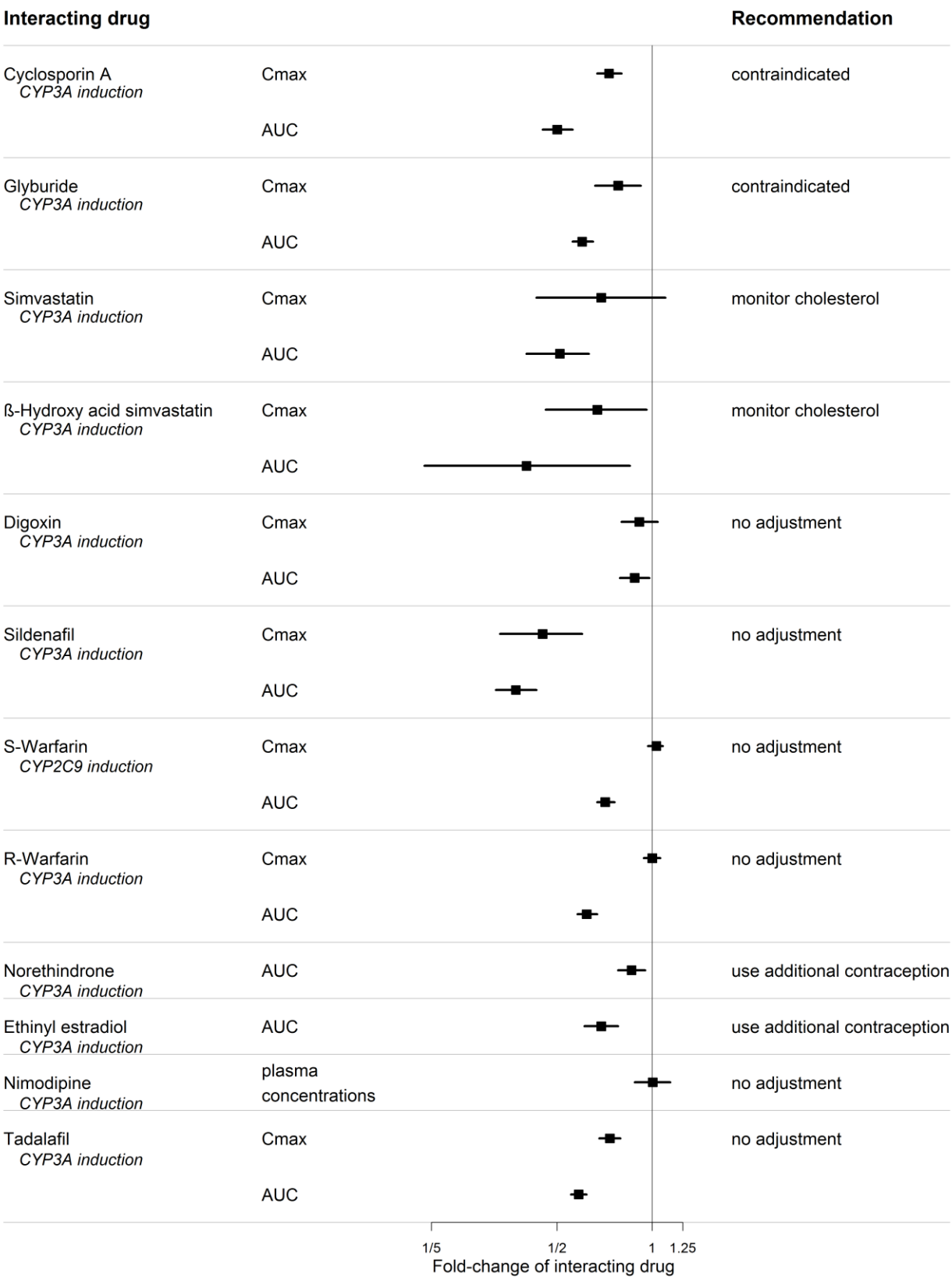
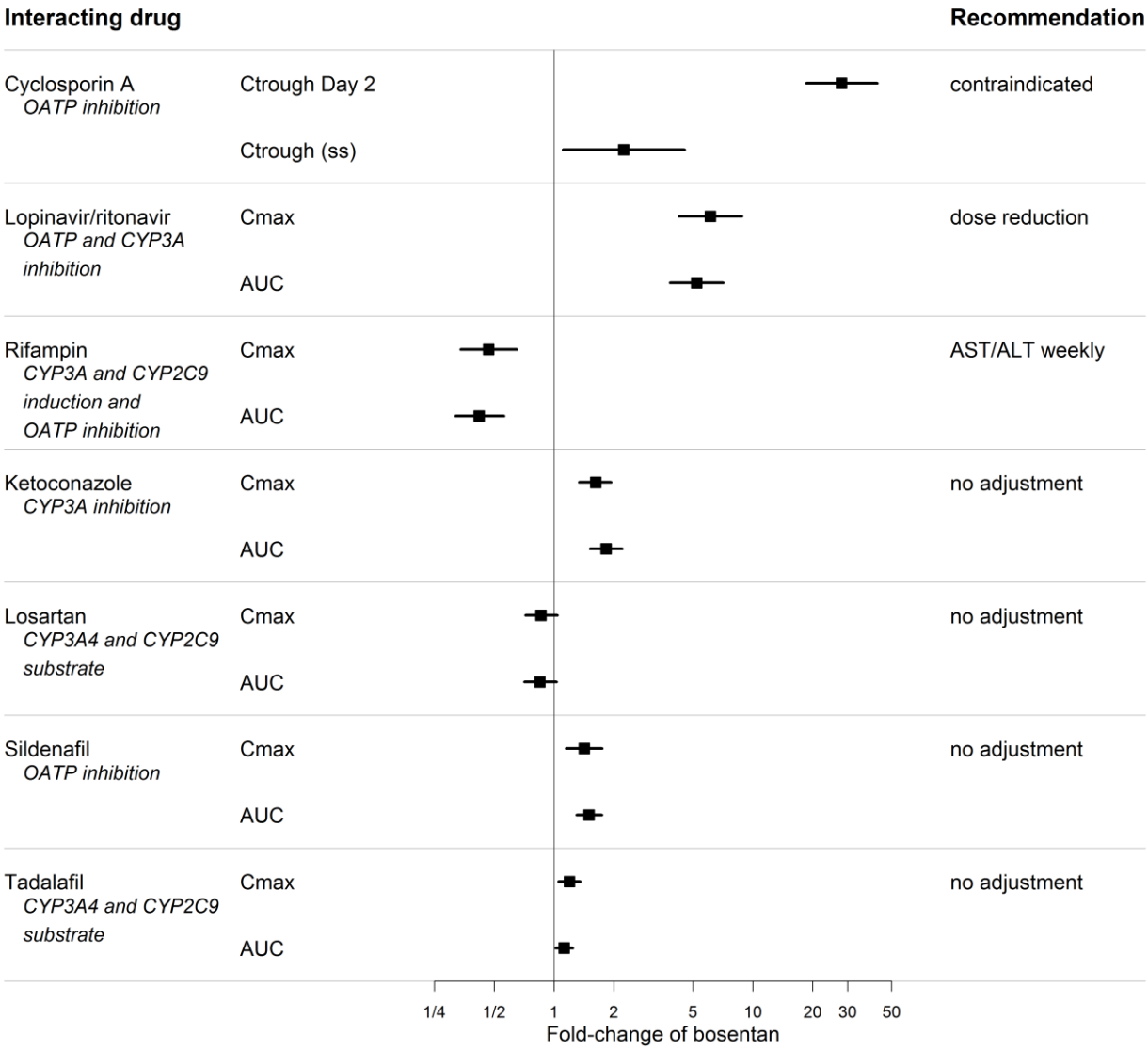


Figure 4. Effects of other drugs on bosentan



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^2 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.

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^2 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) PAH: idiopathic or heritable PAH (72%) or PAH associated with scleroderma or other connective tissue diseases (21%), or to autoimmune diseases (7%). There were no patients with PAH 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 4.

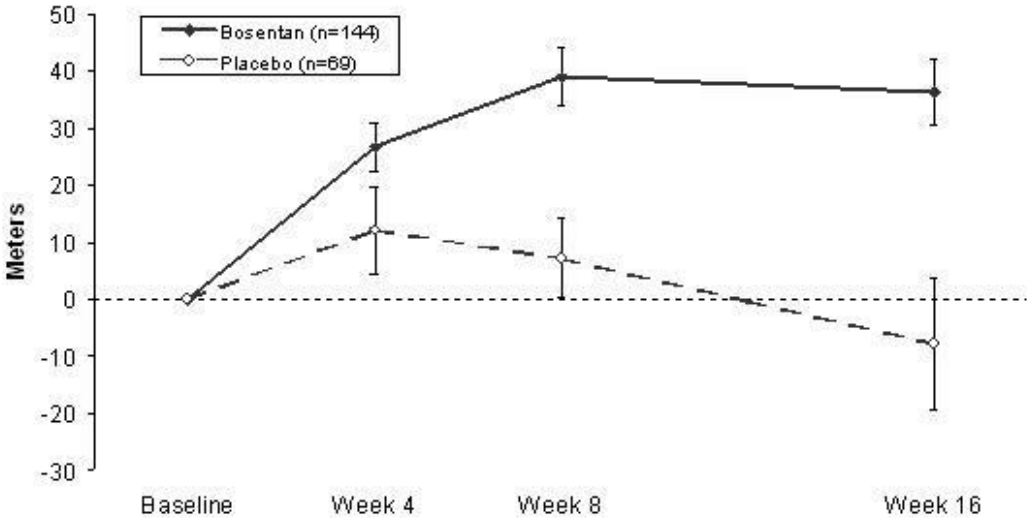
Table 4. Effects of Tracleer on 6-minute walk distance

	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)**
Baseline	326 ± 73	333 ± 75	344 ± 76	360 ± 86	355 ± 82
End point	353 ± 115	379 ± 101	336 ± 129	431 ± 66	350 ± 147
Change from baseline	27 ± 75	46 ± 62	-8 ± 96	70 ± 56	-6 ± 121
Placebo – subtracted	35 [(a)]	54 [(b)]		76 [(c)]	

Distance in meters: mean ± standard deviation. Changes are to week 16 for BREATHE-1 and to week 12 for Study 351.
[(a)]p=0.01; by Wilcoxon;[(b)]p=0.0001; by Wilcoxon; [(c)]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 5). 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 5. 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 5).

The relationship between hemodynamic effects and improvements in 6-minute walk distance is unknown.

Table 5: Change from Baseline to Week 12: Hemodynamic Parameters

	Tracleer 125 mg twice daily		Placebo
CI (L/min/m^2)	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[a]	
Mean PAP (mmHg)	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]	
PVR (dyn•sec•cm^{-5})	n=19		n=10
Baseline	896±425		942±430
Absolute Change	-223±245		191±235
Treatment Effect		-415[a]	
Mean RAP (mmHg)	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[a]	

Values shown are means ± SD
[a]$p \leq 0.001$; [b]$p < 0.02$

Symptoms and Functional Status

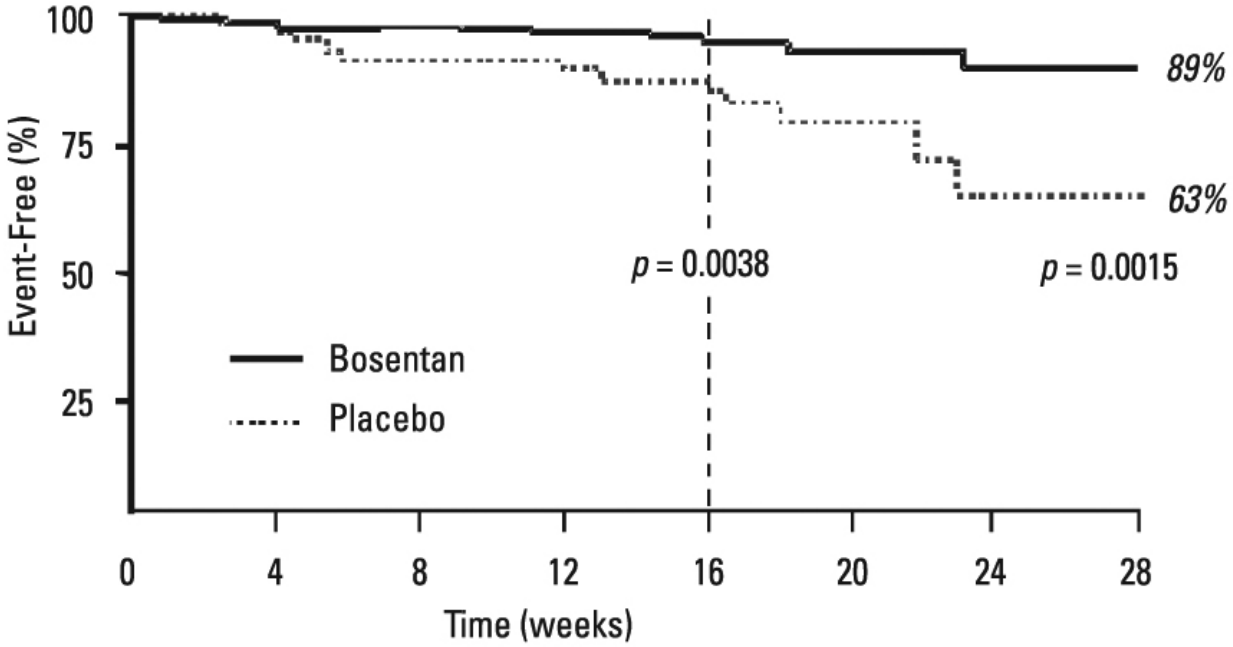
Symptoms of PAH were assessed by Borg dyspnea score, WHO functional class, and rate of "clinical worsening." Clinical worsening was assessed as the sum of death, hospitalizations for PAH, discontinuation of therapy because of PAH, and need for epoprostenol. There was a significant reduction in dyspnea 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 6 and Figure 6). Figure 6 shows the log-rank test reflecting clinical worsening over 28 weeks.

Table 6. Incidence of Clinical Worsening, Intent To Treat Population

	BREATHE-1		Study 351	
	Tracleer 125/250 mg twice daily (n = 144)	**Placebo (n = 69)**	**Tracleer 125 mg twice daily (n = 21)**	**Placebo (n = 11)**
Patients with clinical worsening [n (%)]	9 (6%)[a]	14 (20%)	0 (0%)[b]	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[c]	4 (3%)	3 (4%)	0 (0%)	3 (27%)

Note: Patients may have had more than one reason for clinical worsening.
[a]p=0.0015 vs. placebo by log-rank test. There was no relevant difference between the 125 mg and 250 mg twice daily groups.
[b]p=0.033 vs. placebo by Fisher's exact test.
[c]Receipt of epoprostenol was always a consequence of clinical worsening.

Figure 6. 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.

Pediatric Studies

The efficacy of bosentan was evaluated in an open-label, uncontrolled study in 19 pediatric patients with PAH aged 3 to 15 years. Patients had primary pulmonary hypertension (n = 10) or PAH related to congenital heart diseases (9 patients) and were WHO functional class II (n = 15, 79%) or class III (n = 4; 21%) at baseline. Patients were dosed with bosentan at approximately 2 mg/kg twice daily (body weight adjusted dose, corresponding to the recommended adult dose) *[see Dosage and Administration (2.1)]* for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study.

Hemodynamics were measured in 17 patients (Table 7). The mean decrease in PVR was 389 dyn·sec·cm^{-5}, which was similar to the effect seen in adults. Hemodynamic improvements from baseline were similar with or without co-administration of epoprostenol.

Table 7: Change from Baseline to Week 12: Hemodynamic Parameters

	Tracleer 2 mg/kgtwice daily
CI (L/min/m^2)	n=17
Baseline	4.0±1.5
Absolute Change	0.5±1.4
Mean PAP (mmHg)	n=18
Baseline	60±18
Absolute Change	-8±9
PVR (dyn•sec•cm^{-5})	n=17
Baseline	1195±755
Absolute Change	-389±616
Mean RAP (mmHg)	n=18
Baseline	6.1±2.7
Absolute Change	-0.5±2.3

Values shown are means ± SD

Pulmonary Arterial Hypertension in Adults 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 in adult 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, debossed 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, debossed 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.

32 mg tablets for oral suspension, pale yellow to off-white, clover-shaped, quadrisected on one side and debossed with “32” on the other side, packaged in child resistant Aluminum/Aluminum peel-push blisters.

NDC 66215-103-56: Carton of 56 tablets for oral suspension in 4 blister-strips of 14 tablets.

NDC 66215-103-14: Blister strip of 14 tablets for oral suspension.

Store at 20ºC – 25ºC (68ºF – 77ºF). Excursions are permitted between 15°C and 30°C (59°F and 86°F). [See USP Controlled Room Temperature]. These storage temperatures apply to both film-coated and dispersible tablets. Divided dispersible tablets should be stored under the same conditions and used within 7 days. Tablet pieces may be returned to the opened blister and stored there out of reach of children for up to 7 days.

Manufactured for:

Actelion Pharmaceuticals US, Inc.

South San Francisco, CA 94080, USA

ACT20180423

17. PATIENT COUNSELING INFORMATION

Advise the patient to read the 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 the Tracleer REMS Program.

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

- **Lactation**

  Advise women not to breastfeed during treatment with TRACLEER *[see Use in Specific Populations (8.2)]*.

- **Infertility**

Advise males of reproductive potential that TRACLEER may impair fertility *[see Warnings and Precautions (5.6), Adverse Reactions (6.1), Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)]*.

- **Phenylketonurics**

  Tracleer dispersible tablets contain phenylalanine, a component of aspartame. Each dispersible tablet contains 1.87 mg of phenylalanine.

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

Administration Considerations

Advise patients that Tracleer dispersible tablets should not be split into quarters.