

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

Initial U.S. Approval: 2001

WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

See full prescribing information for complete boxed warning.

Tracleer can be prescribed and dispensed only through a restricted distribution program (Tracleer Access Program) because of these risks:

Elevations of liver aminotransferases (ALT, AST) and liver failure have been reported with Tracleer (5.1).

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

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

- Must exclude pregnancy before and during treatment (4.1, 8.1).
- To prevent pregnancy, females of childbearing potential must use two reliable forms of contraception during treatment and for one month after stopping Tracleer (2.4, 8.1).

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 predominately 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 systemic-to-pulmonary shunts (18%) (1.1).

Considerations for use:

Consider whether benefits offset the risk of liver injury in WHO Class II patients. Early liver injury 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 (2.6).
- Reduce the dose and closely monitor patients developing aminotransferase elevations >3 X ULN (2.2).
- Discontinue Tracleer 36 hours prior to initiation of ritonavir. Patients on ritonavir: Initiate Tracleer at 62.5 mg once daily or every other day (2.7).

DOSAGE FORMS AND STRENGTHS

- 62.5 mg and 125 mg unscored tablets (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. Use with caution in mild impairment (5.2).
- Fluid retention: May require intervention (5.3).
- Decreased sperm counts: it cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis. (5.4)
- Decreases in hemoglobin and hematocrit: Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter (5.5).
- Pulmonary veno-occlusive disease: If signs of pulmonary edema occur, consider the possibility of underlying pulmonary veno-occlusive disease and discontinue treatment if necessary (5.6).

ADVERSE REACTIONS

Most common ($\geq 3\%$) placebo-adjusted adverse reactions are respiratory tract infection and anemia (6.1).

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

DRUG INTERACTIONS

- Hormonal contraceptives: Use with Tracleer decreases exposure and reduces contraceptive effectiveness (7.2).
- Cyclosporine A, glyburide: Concomitant administration of each drug with Tracleer is contraindicated (7.3, 7.4).
- Simvastatin and other CYP3A-metabolized statins: Combination use decreases statin levels and may reduce efficacy (7.6).
- Rifampin: Alters bosentan levels. Monitor hepatic function weekly for 4 weeks, followed by normal monitoring (7.7).

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue nursing or the drug taking into consideration the importance of the drug to the mother (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide Revised: 2/2011

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WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

Because of the risk of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1 866 228 3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. [*see Warnings and Precautions (5.7)*].

Liver Injury

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 liver injury, 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 co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.

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

Elevations in aminotransferases require close attention [*see Dosage and Administration (2.2)*]. Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (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 re-introduction of Tracleer in these circumstances.

Teratogenicity

Tracleer is likely to cause major birth defects if used by pregnant females based on animal data [*see Contraindications (4.1)*]. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. 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)*]. Monthly pregnancy tests should be obtained.

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 predominately 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 systemic-to-pulmonary 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 liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

2. DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased 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 liver injury.

Tablets should be administered morning and evening with or without food.

2.2 Required Monitoring

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated.

2.3 Dosage Adjustments for Patients Developing Aminotransferase Elevations

The table below summarizes the dosage adjustment and monitoring recommendations for patients who develop aminotransferase elevations >3 X ULN during therapy with Tracleer. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (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 re-introduction of Tracleer in these circumstances.

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

| ALT/AST levels | Treatment and monitoring recommendations |
|-----------------------|--|
| > 3 and ≤ 5 x ULN | Confirm by another aminotransferase test; if confirmed, reduce the daily dose to 62.5 mg twice daily or interrupt treatment, and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values, continue or re-introduce the treatment as appropriate (see below). |
| > 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 pre-treatment values, consider re-introduction of the treatment (see below). |
| > 8 x ULN | Treatment should be stopped and re-introduction of Tracleer should not be considered. There is no experience with re-introduction 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.

2.4 Use in Females of Childbearing Potential

Initiate treatment in females of child-bearing potential only after a negative pregnancy test and only in females who are using two reliable methods of contraception. Females who have had a tubal sterilization or a Copper T 380A IUD or LNG 20 IUS inserted do not require other forms of contraception. Effective contraception must be practiced throughout treatment and for one month after stopping Tracleer. Females should seek contraceptive advice as needed from a gynecologist or similar expert. Urine or serum pregnancy tests should be obtained monthly in females of childbearing potential taking Tracleer [*see Boxed Warning, Contraindications (4.1), Drug Interactions (7.2)*].

2.5 Use in Patients with Pre-existing Hepatic Impairment

Tracleer should generally be avoided in patients with moderate or severe liver impairment. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function [*see Warnings and Precautions (5.2)*].

2.6 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.

2.7 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 62.5 mg once daily or every other day based upon individual tolerability [*see Drug Interactions (7.5)*].

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 62.5 mg once daily or every other day based upon individual tolerability [*see Dosage and Administration (2.8) and Drug Interactions (7.5)*].

2.8 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

Tracleer is available as 62.5 mg and 125 mg film-coated, unscored tablets for oral administration.

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

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

4. CONTRAINDICATIONS

4.1 Pregnancy Category X

*[see **BOXED WARNING**]*

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. In animal studies, bosentan caused teratogenic effects including malformations of the head, mouth, face, and large blood vessels. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of child bearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. Monthly pregnancy tests should also be obtained. If this drug is used during pregnancy or

if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. [\[see 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 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 co-administration 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 rash and angioedema [\[see Adverse Reactions \(6.2\)\]](#).

5 WARNINGS AND PRECAUTIONS

5.1 Potential Liver Injury

Elevations in ALT or AST by more than 3 x ULN were observed in 11% of bosentan-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 bosentan. The combination of hepatocellular injury (increases in aminotransferases of > 3 x ULN) and increases in total bilirubin (≥ 3 x ULN) is a marker for potential serious liver injury.

Elevations of AST and/or ALT associated with bosentan 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. If elevated aminotransferase levels are seen, changes in monitoring and treatment must be initiated. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment should be stopped. There is no experience with the re-introduction of Tracleer in these circumstances [\[see Dosage and Administration \(2.2\)\]](#).

5.2 Patients with Pre-existing Hepatic Impairment

Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see *Dosage and Administration (2.5)*]. In addition, Tracleer should generally be avoided in patients with elevated aminotransferases ($> 3 \times \text{ULN}$) because monitoring liver injury in these patients may be more difficult [see *Boxed Warning*].

5.3 Fluid Retention

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of 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 [see *Clinical Studies (14.2)*].

In addition, there have been numerous post-marketing 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 therapy.

5.4 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 two 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.

5.5 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 bosentan-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 bosentan treatment and hemoglobin levels stabilized by 4–12 weeks of bosentan treatment. In placebo-controlled studies of all uses of bosentan, marked decreases in hemoglobin (> 15% decrease from baseline resulting in values < 11 g/dL) were observed in 6% of bosentan-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 bosentan-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 bosentan treatment.

During the course of treatment the hemoglobin concentration remained within normal limits in 68% of bosentan-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.

5.6 Pulmonary Veno-Occlusive Disease

Should signs of pulmonary edema occur when Tracleer is administered, the possibility of associated pulmonary veno-occlusive disease should be considered and Tracleer should be discontinued.

5.7 Prescribing and Distribution Program for Tracleer

Because of the risks of liver injury and birth defects, Tracleer is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.). Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute Tracleer. In addition, Tracleer may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P. Information about Tracleer and T.A.P. can be obtained by calling 1-866-228-3546.

To enroll in T.A.P., prescribers must complete the T.A.P. Tracleer (bosentan) Enrollment and Renewal Form (see T.A.P. Tracleer (bosentan) Enrollment and Renewal Form for full prescribing physician agreement) indicating agreement to:

- Read and understand the communication and educational materials for prescribers regarding the risks of Tracleer.
- Review and discuss the Tracleer Medication Guide and the risks of bosentan (including the risks of teratogenicity and hepatotoxicity) with every patient prior to prescribing Tracleer.
- Review pretreatment liver function tests (ALT/AST/bilirubin) and, for females of childbearing potential, confirm that the patient is not pregnant.
- Agree to order and monitor monthly liver function tests and, for females of childbearing potential, pregnancy tests.
- Enroll all patients in T.A.P. and renew patients' enrollment annually thereafter.

- Educate and counsel females of childbearing potential to use reliable contraception, as defined on the Tracleer Enrollment and Renewal Form, during treatment with Tracleer and for one month after treatment discontinuation.
- Counsel patients who fail to comply with the program requirements.
- Notify Actelion Pharmaceuticals US, Inc. of any adverse events, including liver injury, and report any pregnancy during Tracleer treatment.

Throughout treatment and for one month after stopping Tracleer, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. 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.

6. ADVERSE REACTIONS

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

- Potential liver injury *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Fluid retention *[see Warnings and Precautions (5.3)]*

6.1 Clinical Studies Experience

Safety data on bosentan 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 bosentan 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 bosentan ranged from 1 day to 1.7 years (N=174 more than 6 months and N=28 more than 12 months).

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.

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 bosentan (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 bosentan was abnormal liver function.

The adverse drug events that occurred in $\geq 3\%$ of the bosentan-treated patients and were more common on bosentan 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 $\geq 3\%$ of patients treated with bosentan 125-250 mg twice daily and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

| <i>Adverse Event</i> | Bosentan 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% |
| Liver Function Test 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.
Combined data from Study-351, BREATHE-1 and EARLY

6.2 Postmarketing Experience

There have been several post-marketing reports of angioedema associated with the use of bosentan. 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 post approval 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 *[see Contraindications (4.4)]*

Thrombocytopenia

Rash

Jaundice

Anemia requiring transfusion

Neutropenia and leukopenia

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 bosentan 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.

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 Boxed Warning, Contraindications (4.1)*].

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.

7.3 Cyclosporine A

The concomitant administration of bosentan 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. Co-administration 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)*].

Co-administration of bosentan decreased the plasma concentrations of glyburide by approximately 40%. The plasma concentrations of bosentan were also decreased by approximately 30%. Bosentan 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, co-administration 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 (2.7)*].

Co-administration of Tracleer 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

Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A substrate), and its active β -hydroxy acid metabolite, by approximately 50%. The plasma concentrations of bosentan were not affected. Bosentan 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

Co-administration 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 bosentan on rifampin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure liver function weekly for the first 4 weeks before reverting to normal monitoring.

7.8 Tacrolimus

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

7.9 Ketoconazole

Co-administration 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 bosentan is necessary, but increased effects of bosentan should be considered.

7.10 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 bosentan 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 bosentan- 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, 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 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 this drug is used during pregnancy or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Females of childbearing 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 childbearing 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.

Drug interaction studies show that Tracleer 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 childbearing potential using Tracleer must use two reliable forms of contraception unless she has a tubal sterilization or has a Copper T 380A IUD or LNG 20 IUS. In these cases, no additional contraception is needed. Contraception should be continued until one month after completing Tracleer therapy. Females of childbearing 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/m² 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/m² 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 teratogenicity is a class effect of these drugs [*see Nonclinical Toxicology (13.1)*].

8.3 Nursing mothers

It is not known whether Tracleer 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 Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug 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. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients

given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

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. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment [*see Dosage and Administration (2.5), Warnings and Precautions (5.2), 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)*].

8.8 Patients with Low Body Weight

[*See Dosage and Administration (2.6)*].

10. OVERDOSAGE

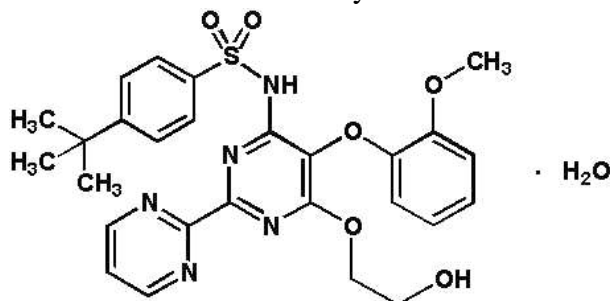
Bosentan has been given as a single dose of up to 2400 mg in normal volunteers, or up to 2000 mg/day for 2 months in patients, without any major clinical consequences. The most common side effect was headache of mild to moderate intensity. In the cyclosporine A interaction study, in which doses of 500 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 bosentan 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

Bosentan is an endothelin receptor antagonist, belonging 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

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 pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. 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.

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, body weight, 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 (as indicated by the Child-Pugh method) to 8 controls, the single- and multiple-dose pharmacokinetics of bosentan was not altered in patients with mild hepatic impairment. The influence of moderate or severe liver impairment on the pharmacokinetics of bosentan has not been evaluated. Bosentan should generally be avoided in patients with moderate or severe liver abnormalities and/or elevated aminotransferases >3 x ULN [[see Dosage and Administration \(2.5\), Warnings and Precautions \(5.2\)](#)].

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/m² 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 ≥ 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 teratogenicity 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/m² 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.

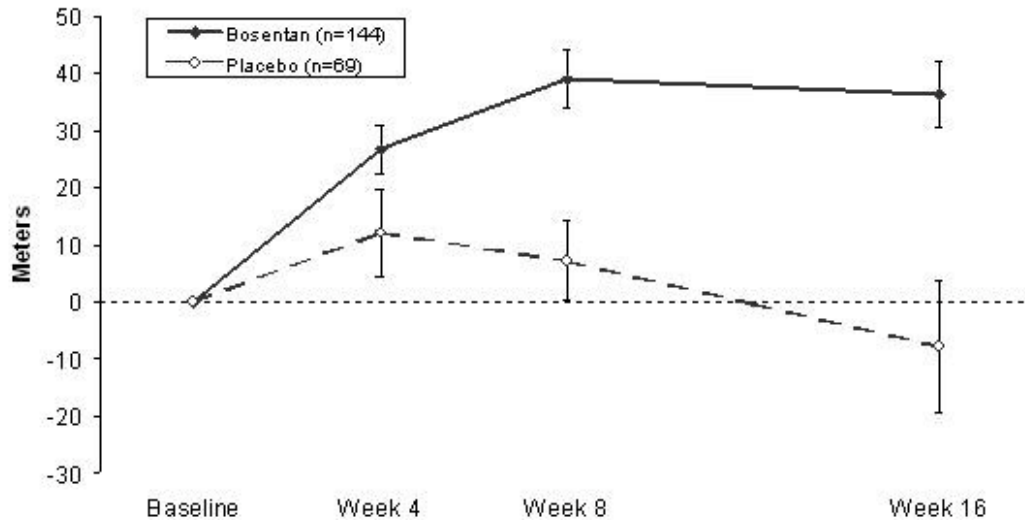
Table 3. Effects of bosentan on 6-minute walk distance

| | BREATHE-1 | | | Study 351 | |
|---------------------------------|---|---|---------------------|---|---------------------|
| | Bosentan 125 mg twice daily (n = 74) | Bosentan 250 mg twice daily (n = 70) | Placebo (n = 69) | Bosentan 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 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 liver injury 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 bosentan (125 mg twice daily and 250 mg twice daily) groups. Values are expressed as mean \pm 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

| | Bosentan 125 mg twice daily | Placebo |
|---|------------------------------------|---------------------|
| Mean CI (L/min/m²) | N=20 | N=10 |
| Baseline | 2.35 \pm 0.73 | 2.48 \pm 1.03 |
| Absolute Change | 0.50 \pm 0.46 | -0.52 \pm 0.48 |
| Treatment Effect | | 1.02 ^(a) |
| Mean PAP (mmHg) | N=20 | N=10 |
| Baseline | 53.7 \pm 13.4 | 55.7 \pm 10.5 |
| Absolute Change | -1.6 \pm 5.1 | 5.1 \pm 8.8 |
| Treatment Effect | | -6.7 ^(b) |
| Mean PVR (dyn\cdotsec\cdotcm⁻⁵) | N=19 | N=10 |
| Baseline | 896 \pm 425 | 942 \pm 430 |
| Absolute Change | -223 \pm 245 | 191 \pm 235 |
| Treatment Effect | | -415 ^(a) |
| Mean RAP (mmHg) | N=19 | N=10 |
| Baseline | 9.7 \pm 5.6 | 9.9 \pm 4.1 |
| Absolute Change | -1.3 \pm 4.1 | 4.9 \pm 4.6 |
| Treatment Effect | | -6.2 ^(a) |

Values shown are means \pm SD
^(a)p \leq 0.001; ^(b)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

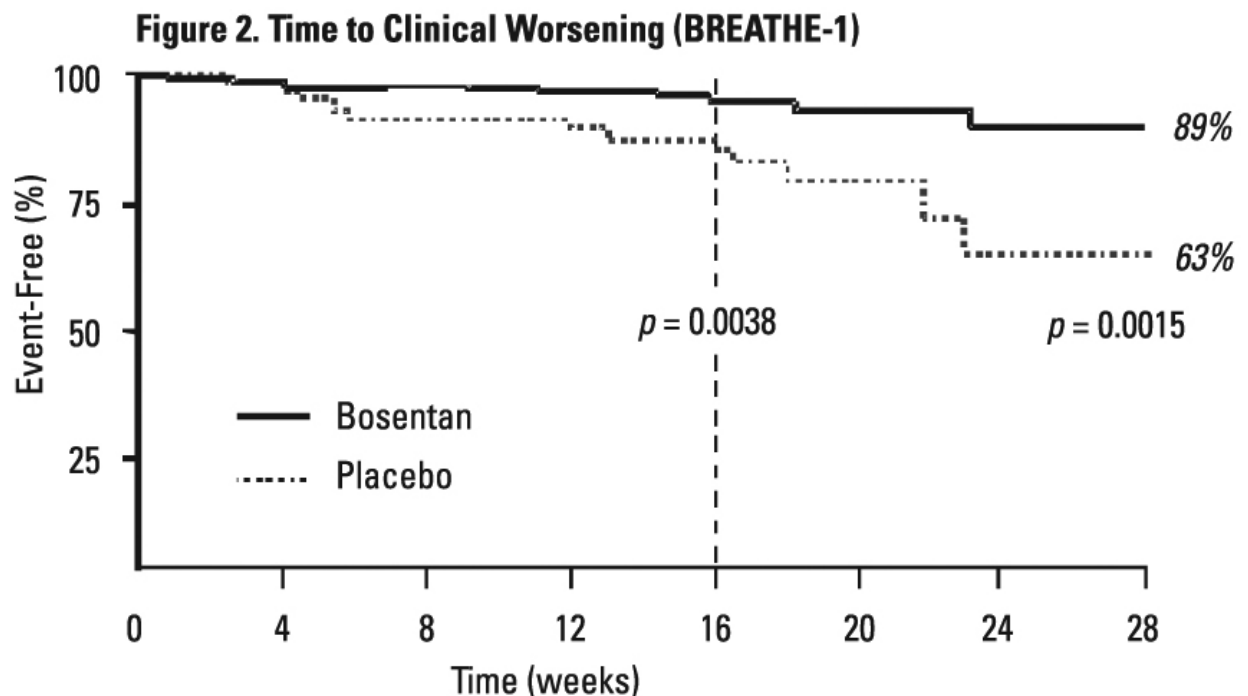
| | BREATHE-1 | | Study 351 | |
|---|--|---------------------|---|---------------------|
| | Bosentan 125/250 mg twice daily (N = 144) | Placebo (N = 69) | Bosentan 125 mg twice daily (N = 21) | Placebo (N = 11) |
| Patients with clinical worsening [n (%)] | 9 (6%) ^(a) | 14 (20%) | 0 (0%) ^(b) | 3 (27%)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



Time from randomization to clinical worsening with Kaplan-Meier estimate of the proportions of failures in BREATHE-1. All patients (N=144 in the bosentan 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 bosentan 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 bosentan 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 co-primary 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, bosentan treatment was associated with a reduced incidence of worsening of at least one functional class (3% bosentan vs. 13% placebo, p = 0.03), and improvement in hemodynamic variables (PVR, mPAP, TPR, cardiac index, and SVO₂; p < 0.05). The + 19 m mean (+14 m median) increase in 6-minute walk distance with bosentan 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 bosentan 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 Systemic-to-Pulmonary Shunts

A small study with patients (n=54) with Eisenmenger physiology demonstrated effects of bosentan 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 bosentan 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.

NDC 66215-101-06: Bottle containing 60 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.

NDC 66215-102-06: Bottle containing 60 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

ACT20101217

17. PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer [[see Medication Guide \(17.2\)](#)].

17.1 Important Information

- Monthly monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.

- Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNG 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

- Drug Interactions

The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

17.2 Medication Guide

See accompanying Medication Guide

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 Access Program (T.A.P.). Before you begin taking Tracleer, you must read and agree to all of the instructions in T.A.P.

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 a blood test 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 and each month during Tracleer treatment.**
- Talk with your healthcare provider or gynecologist (a doctor who specializes in female reproduction) to find out about how to prevent pregnancy. Do not have unprotected sex. Tell your healthcare provider right away if you miss a menstrual period or think you may be pregnant.
- Females who are able to get pregnant must use birth control (contraception) during Tracleer treatment. **You must choose and use two reliable forms of birth**

control at the same time, unless you have had a tubal sterilization, or have a Copper T 380A IUD or LNG 20 IUS. These methods can be used alone.

Talk with your healthcare provider about which 2 methods of reliable birth control you should use. Your healthcare provider may recommend that you use a different method of birth control to help lower your risk of problems with your pulmonary arterial hypertension. See the end of this Medication Guide for more information about reliable methods of contraception during treatment with Tracleer.

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 T.A.P.
- available to people who understand and agree to enroll in T.A.P.

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?”
- have a blood test that shows possible liver injury.
- take one of these medicines:
 - cyclosporine A used for psoriasis and rheumatoid arthritis, and to prevent rejection of heart or kidney transplants
 - glyburide used for diabetes
- you are allergic to any of the ingredients in Tracleer. See the end of this Medication Guide for a 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 breast-feed. You should not do both.
- **Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription 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.

How should I take Tracleer?

Your healthcare provider will give you detailed information about T.A.P..

- 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 are:

- 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 68°F to 77°F (20°C-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 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.

| Reliable methods of contraception during treatment with Tracleer | | |
|--|--|---|
| Methods to use alone | Hormone (choose 1 and use with a barrier method) | Barrier (use both OR choose 1 and use with a hormone method) |
| <ul style="list-style-type: none">• Intrauterine devices (IUDs)<ul style="list-style-type: none">— Copper T 380A IUD— LNG-20 IUS (progesterone IUD)• Tubal sterilization | <ul style="list-style-type: none">• Estrogen and progesterone<ul style="list-style-type: none">— Oral contraceptives— Transdermal patch— Vaginal ring• Progesterone only<ul style="list-style-type: none">— Injection— Implant | <ul style="list-style-type: none">• Male condom with spermicide• Diaphragm with spermicide OR Cervical cap with spermicide |
| | A partner's vasectomy still requires 1 additional method of contraception. | |

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