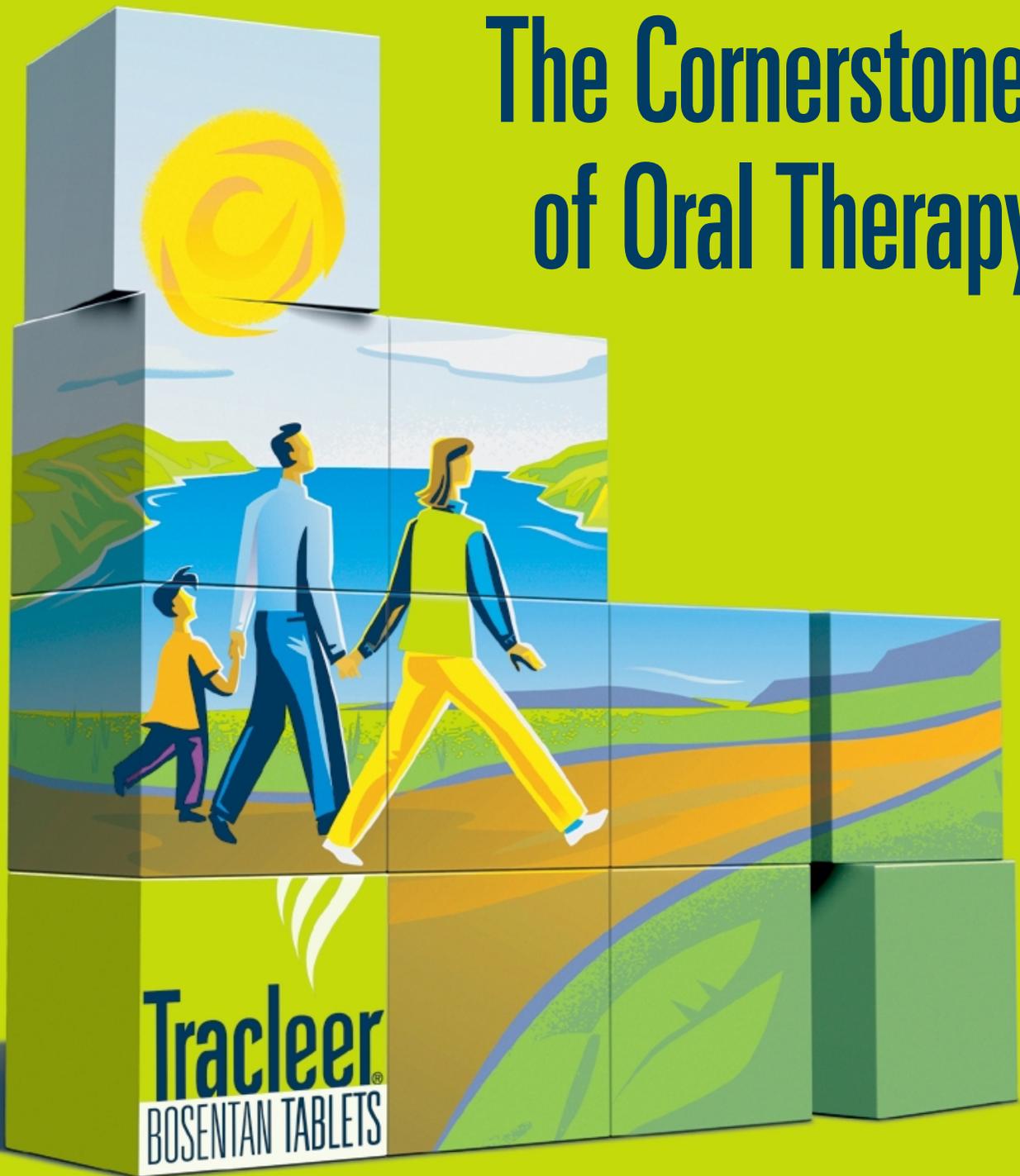


For Patients with Pulmonary Arterial
Hypertension WHO Class III or IV

Tracleer— The Cornerstone of Oral Therapy



Please see the following brief summary of prescribing information.

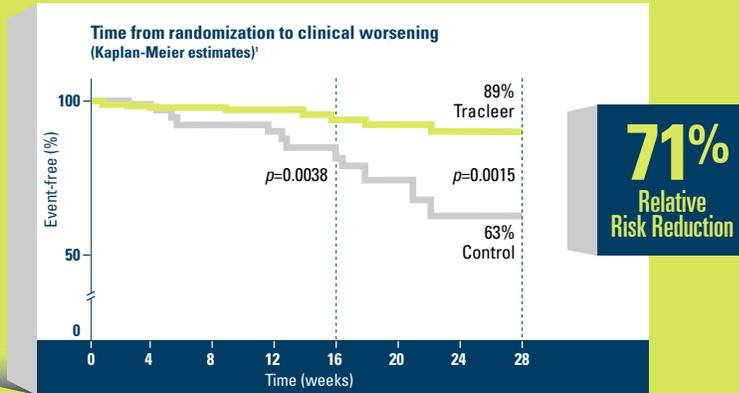
In Pulmonary Arterial Hypertension WHO Class III or IV

Start with Tracleer

The oral endothelin receptor antagonist backed by long-term data

- Improves exercise ability
- Improves hemodynamics (CI, PAP, PVR, RAP)

Reduces risk of clinical worsening



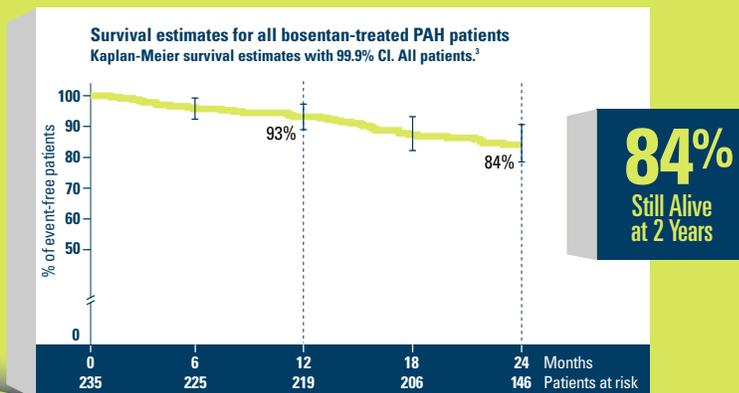
BREATHE-1 All patients (n=144 in the Tracleer group and n=69 in the control group) participated in the first 16 weeks. A subset of this population (n=35 in the Tracleer group and n=13 in the control group) continued for up to 28 weeks.

Tracleer significantly reduced risk of clinical worsening by 71% relative to control at week 28.¹

- Clinical worsening defined as combined endpoint of death, hospitalization or discontinuation due to worsening PAH, or initiation of epoprostenol therapy¹
- A statistically significant difference was apparent as early as week 16¹
- Treatment effect was notable because control groups received placebo plus current therapy, which excluded IV epoprostenol but could include²:
 - Vasodilators
 - Calcium channel blockers
 - ACE inhibitors
 - Digoxin
 - Diuretics
 - Anticoagulants

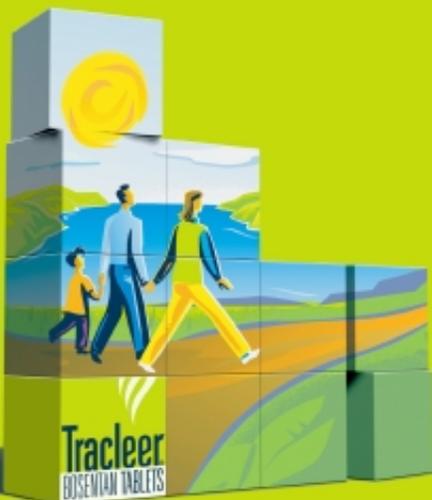
Stay with Tracleer

Long-term data for patients treated with Tracleer



In the 2 Tracleer pivotal trials and their open-label extensions (n=235), 93% and 84% of patients were still alive at 1 year and 2 years, respectively, after the start of treatment with Tracleer.²

- Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival²
- These estimates may be influenced by the presence of epoprostenol treatment, which was administered to 43 of the 235 patients²
- Patients in the Tracleer trials may have also been receiving vasodilators (calcium channel blockers or ACE inhibitors), digoxin, anticoagulants, and/or diuretics²



Liver and pregnancy warnings

- Requires attention to two significant concerns
 - Potential for serious liver injury: Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter
 - High potential for major birth defects: Pregnancy must be excluded and prevented by two forms of birth control; monthly pregnancy tests should be obtained
- Contraindicated for use with cyclosporine A and glyburide

Tracleer may be prescribed only through the Tracleer Access Program (T.A.P.) by calling 1-866-228-3546.

The Cornerstone of Oral Therapy



www.TRACLEER.com



Please see brief summary of prescribing information and full reference list on following page.

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62.5 mg and 125 mg film-coated tablets

Brief Summary: Please see package insert for full prescribing information.

Use of TRACLEER® requires attention to two significant concerns: 1) potential for serious liver injury, and 2) potential damage to a fetus.

WARNING: Potential liver injury. TRACLEER® causes 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 WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). To date, in a setting of close monitoring, elevations have been reversible, within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae. Elevations in aminotransferases require close attention (see DOSAGE AND ADMINISTRATION). 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 should be stopped. There is no experience with the re-introduction of TRACLEER® in these circumstances.

CONTRAINDICATION: Pregnancy. TRACLEER® (bosentan) is very likely to produce major birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER® and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving TRACLEER® (see Precautions: Drug Interactions). Monthly pregnancy tests should be obtained.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER® (bosentan) as small as possible, TRACLEER® may be prescribed only through the TRACLEER® Access Program by calling 1 866 228 3546. Adverse events can also be reported directly via this number.

INDICATIONS AND USAGE: TRACLEER® is indicated for the treatment of pulmonary arterial hypertension in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

CONTRAINDICATIONS: TRACLEER® is contraindicated in pregnancy, with concomitant use of cyclosporine A, with co-administration of glyburide, and in patients who are hypersensitive to bosentan or any component of the medication.

Pregnancy Category X. TRACLEER® is expected to cause fetal harm if administered to pregnant women. 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. There are no data on the use of TRACLEER® in pregnant women. TRACLEER® should be started only in patients known not to be pregnant. For female patients of childbearing potential, a prescription for TRACLEER® should not be issued by the prescriber unless the patient assures the prescriber that she is not sexually active or provides negative results from a 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 women of childbearing potential taking TRACLEER®. The patient must be advised that if there is any delay in onset of menses or any other reason to suspect pregnancy, she should notify the physician immediately for pregnancy testing. If the pregnancy test is positive, the physician and patient must discuss the risk to the pregnancy and to the fetus.

WARNINGS: 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). 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 to date have been reversible after treatment interruption or cessation. These aminotransferase elevations 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. *Pre-existing Liver Impairment:* TRACLEER® should generally be avoided in patients with moderate or severe liver impairment. In addition, TRACLEER® should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) because monitoring liver injury in these patients may be more difficult.

PRECAUTIONS: Hematologic Changes: Treatment with TRACLEER® caused a dose-related decrease in hemoglobin and hematocrit. 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 of < 11 g/dl) were observed in 6% of bosentan-treated patients and 3% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg b.i.d., 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 28% of placebo-treated patients. In 80% of cases, 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. 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. *Fluid retention:* 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®. 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.

Information for Patients: Patients are advised to consult the TRACLEER® Medication Guide on the safe use of TRACLEER®. The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases and urine or serum pregnancy testing and of avoidance of pregnancy. The physician should discuss options for effective contraception and measures to prevent pregnancy with their female patients. Input from a gynecologist or similar expert on adequate contraception should be sought as needed.

Drug Interactions: Bosentan is metabolized by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan. Bosentan is an inducer of CYP3A4 and CYP2C9. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes will be decreased when TRACLEER® is co-administered. Contraceptives: Specific interaction studies have not been performed to evaluate the effect of co-administration of bosentan and hormonal contraceptives, including oral, injectable or implantable contraceptives. Since many of these drugs are metabolized by CYP3A4, there is a possibility of failure of contraception when TRACLEER® is co-administered. Women should not rely on hormonal contraception alone when taking TRACLEER®. Cyclosporine A: During the first day of concomitant administration, trough concentrations of bosentan were increased by about 30-fold. Steady-state bosentan plasma concentrations were 3- to 4-fold higher than in the absence of cyclosporine A (see CONTRAINDICATIONS). Tacrolimus: Co-administration of tacrolimus and bosentan has not been studied in man. 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. Glyburide: An increased risk of elevated liver aminotransferases was observed in patients receiving concomitant therapy with glyburide (see CONTRAINDICATIONS). Alternative hypoglycemic agents should be considered. Bosentan is also expected to reduce plasma concentrations of other oral hypoglycemic agents that are predominantly metabolized by CYP2C9 or CYP3A4. The possibility of worsened glucose control in patients using these agents should be considered. Ketoconazole: Co-administration of bosentan 125 mg b.i.d. and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan by approximately 2-fold. No dose adjustment of bosentan is necessary, but increased effects of bosentan should be considered. Simvastatin and Other Statins: Co-administration of bosentan decreased the plasma concentrations of simvastatin (a CYP3A4 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 have significant metabolism by CYP3A4, eg, lovastatin and atorvastatin. The possibility of reduced statin efficacy should be considered. Patients using CYP3A4 metabolized statins should have cholesterol levels monitored after TRACLEER® is initiated to see whether the statin dose needs adjustment. Warfarin: Co-administration of bosentan 500 mg b.i.d. for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 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. Digoxin, Nimodipine and Losartan: Bosentan has been shown to have no pharmacokinetic interactions with digoxin and nimodipine, and losartan has no effect on plasma levels of bosentan.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses about 8 times the maximum recommended human dose [MRHD] of 125 mg b.i.d., on a mg/m² basis. In the same study, doses greater than 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 about 16 times the MRHD. Impairment of Fertility/Testicular Function: Many endothelin receptor antagonists have profound effects on the histology and function of the testes in animals. These drugs have been shown to induce atrophy of the seminiferous tubules of the testes and to reduce sperm counts and male fertility in rats when administered for longer than 10 weeks. Where studied, testicular tubular atrophy and decreases in male fertility observed with endothelin receptor antagonists appear irreversible. In fertility studies in which male and female rats were treated with bosentan at oral doses of up to 50 times the MRHD on a mg/m² basis, no effects on sperm count, sperm motility, mating performance or fertility were observed. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as about 4 times the MRHD for two years but not at doses as high as about 50 times the MRHD for 6 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to about 75 times the MRHD or in dogs treated up to 12 months at doses up to about 50 times the MRHD. There are no data on the effects of bosentan or other endothelin receptor antagonists on testicular function in man.

Pregnancy, Teratogenic Effects: Category X

SPECIAL POPULATIONS: Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding while taking TRACLEER® is not recommended. Pediatric Use: Safety and efficacy in pediatric patients have not been established. Use in Elderly Patients: Clinical experience with TRACLEER® in subjects aged 65 or older has not included a sufficient number of such subjects to identify a difference in response between elderly and younger patients.

ADVERSE REACTIONS: Safety data on bosentan were obtained from 12 clinical studies (8 placebo-controlled and 4 open-label) in 777 patients with pulmonary arterial hypertension, and other diseases. 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 (5%; 8/165 patients) than on placebo (3%; 2/80 patients). In this database the only cause of discontinuations > 1%, and occurring more often on bosentan was abnormal liver function. In placebo-controlled studies of bosentan in pulmonary arterial hypertension and for other diseases (primarily chronic heart failure), a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The duration of treatment ranged from 4 weeks to 6 months. For the adverse drug reactions that occurred in ≥ 3% of bosentan-treated patients, the only ones that occurred more frequently on bosentan than on placebo (≥ 2% difference) were headache (16% vs. 13%), flushing (7% vs. 2%), abnormal hepatic function (6% vs. 2%), leg edema (5% vs. 1%), and anemia (3% vs. 1%). Additional adverse reactions that occurred in > 3% of bosentan-treated pulmonary arterial hypertension patients were: nasopharyngitis (11% vs. 8%), hypotension (7% vs. 4%), palpitations (5% vs. 1%), dyspepsia (4% vs. 0%), edema (4% vs. 3%), fatigue (4% vs. 1%), and pruritus (4% vs. 0%).

Long-term Treatment: The long-term follow-up of the patients who were treated with TRACLEER® in the two pivotal studies and their open-label extensions (N=235) shows that 93% and 84% of patients were still alive at 1 and 2 years, respectively, after the start of treatment with TRACLEER®. These estimates may be influenced by the presence of eoprostenol treatment, which was administered to 43/235 patients. Without a control group, these data must be interpreted cautiously and cannot be interpreted as an improvement in survival.

Special Considerations: Patients with Congestive Heart Failure (CHF): Based on the results of a pair of studies with 1613 subjects, bosentan is not effective in the treatment of CHF with left ventricular dysfunction.

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 b.i.d. 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. There is no specific experience of overdosage with bosentan beyond the doses described above. Massive overdosage may result in pronounced hypotension requiring active cardiovascular support.

DOSAGE AND ADMINISTRATION: TRACLEER® treatment should be initiated at a dose of 62.5 mg b.i.d. for 4 weeks and then increased to the maintenance dose of 125 mg b.i.d. Doses above 125 mg b.i.d. 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.

Dosage Adjustment and Monitoring in Patients Developing Aminotransferase Abnormalities

ALT/AST levels	Treatment and monitoring recommendations
> 3 and ≤ 5 x ULN	Confirm by another aminotransferase test; if confirmed, reduce the daily dose 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. 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. Use in Women of Child-bearing Potential: TRACLEER® treatment should only be initiated in women of child-bearing potential following a negative pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable or implantable contraceptives. Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of childbearing potential taking TRACLEER®. Dose Adjustment in Renally Impaired Patients: The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment. Dose Adjustment in Geriatric Patients: Clinical studies of TRACLEER® did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. 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. Dose Adjustment in Hepatically Impaired Patients: The influence of liver impairment on the pharmacokinetics of TRACLEER® has not been evaluated. Because there is *in vivo* and *in vitro* evidence that the main route of excretion of TRACLEER® is biliary, liver impairment would be expected to increase exposure to bosentan. 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. Dose Adjustment in Children: Safety and efficacy in pediatric patients have not been established. Dose Adjustment in 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 b.i.d. Discontinuation of Treatment: 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 b.i.d. for 3 to 7 days) should be considered.

HOW SUPPLIED: 62.5 mg film-coated, round, biconvex, orange-white tablets, embossed with identification marking "62.5" NDC 66215-101-06. Bottle containing 90 tablets. 125 mg film-coated, oval, biconvex, orange-white tablets, embossed with identification marking "125" NDC 66215-102-06. Bottle containing 60 tablets.

Rx only.

STORAGE: 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].

Reference: 1. Zimmerman HJ. *Hepatotoxicity - The adverse effects of drugs and other chemicals on the liver*. Second ed. Philadelphia: Lippincott, 1999.

References for previous page: 1. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:896–903. 2. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. 2003. 3. Data on file, Actelion Pharmaceuticals.

Manufactured by:
Patheon Inc.
Mississauga, Ontario, CANADA

Marketed by:
Actelion Pharmaceuticals US, Inc.
South San Francisco, CA

