

In pulmonary arterial hypertension (PAH)
WHO Class III or IV

Tracleer goes beyond symptomatic relief

Prescribed to over
55,000
patients¹

Reduced risk
of clinical
worsening*

Functional class
improvement*

42%
improved ≥ 1 class

Hemodynamic
improvement[†]

CI-RAP-PVR-PAP

***BREATH-1** Multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of Tracleer (125 mg BID, 250 mg BID) in patients with WHO functional class III or IV PAH (N=213). All patients (n=144, Tracleer group; n=69, control group) participated in the first 16 weeks. A subset of this population (n=35, Tracleer group; n=13, control group) continued for up to 28 weeks. Clinical worsening was defined as the combined endpoint of death, hospitalization for treatment related to PAH, discontinuation of therapy due to worsening PAH, or initiation of epoprostenol therapy.²

WHO functional class status^{1,2} Placebo—Baseline: 94.2% Class III, 5.8% Class IV. Week 16: 0% Class I, 27.5% Class II, 63.8% Class III, 8.7% Class IV. Tracleer—Baseline: 90.3% Class III, 9.7% Class IV. Week 16: 2.1% Class I, 36.1% Class II, 56.3% Class III, 5.6% Class IV.

†Study 351 Randomized, double-blind, placebo-controlled study of Tracleer 125 mg BID in patients with WHO functional class III or IV PAH (N=32).³

RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; PAP, pulmonary arterial pressure

Please visit www.TRACLEER.com to learn more about Tracleer and PAH.

A Cornerstone of
Oral Therapy



Please see brief summary of prescribing information, including boxed warnings, on following page.

Important safety information ■ Because of the associated risks, Tracleer may be prescribed only through the Tracleer Access Program. **Potential for serious liver injury** (including, after prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring)—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 through the use of reliable forms of birth control; monthly pregnancy tests should be obtained.

Contraindicated for use with cyclosporine A, glyburide, lopinavir/ritonavir, and other ritonavir-containing HIV regimens.

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**). In the post-marketing 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 rare 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.

Elevations in aminotransferases require close attention. **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, 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 **PRECAUTIONS: Drug Interactions**). Therefore, effective contraception through additional forms of contraception must be practiced. 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 (WHO Group I) in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.

CONTRAINDICATIONS: See **BOX WARNING** for **CONTRAINDICATION** to use in pregnancy.

Pregnancy Category X. **TRACLEER**® is expected to cause fetal harm if administered to pregnant women. Bosentan was teratogenic in rats given oral doses ≥ 60 mg/kg/day (twice the maximum recommended human oral dose of 125 mg, b.i.d., 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 of 60 and 300 mg/kg/day (2 and 10 times, respectively, the maximum recommended human dose on a mg/m² basis). 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. There are no data on the use of **TRACLEER**® in pregnant women. Pregnancy must be excluded before the start of treatment with **TRACLEER**® and prevented thereafter by use of reliable contraception. It has been demonstrated that hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives may not be reliable in the presence of **TRACLEER**® and should not be used as the sole contraceptive method in patients receiving **TRACLEER**® (see **Drug Interactions: Hormonal Contraceptives, Including Oral, Injectable, Transdermal and Implantable Contraceptives**). Input from a gynecologist or similar expert on adequate contraception should be sought as needed. **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 must 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.

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.

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.

Lopinavir/Ritonavir or Other Ritonavir-Containing HIV Regimens: Co-administration of lopinavir/ritonavir and bosentan resulted in markedly increased plasma concentrations of bosentan. Therefore, concomitant use of **TRACLEER**® and lopinavir/ritonavir or other ritonavir-containing HIV regimens is contraindicated (see **PRECAUTIONS: Drug Interactions**).

Hypersensitivity: **TRACLEER**® is also contraindicated in patients who are hypersensitive to bosentan or any component of the medication.

WARNINGS: Potential Liver Injury (see **BOX WARNING**): 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 PAH patients on 125 mg b.i.d. and 14% of 70 PAH patients on 250 mg b.i.d. Eight-fold increases were seen in 2% of PAH patients on 125 mg b.i.d. and 7% of PAH patients on 250 mg b.i.d. 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.

Pre-existing Liver 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. 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 (see **BOX WARNING**).

Decreased Sperm Counts: An open-label, single arm, multicenter safety study evaluated the effect on testicular function of **TRACLEER**® 62.5 mg b.i.d. for 4 weeks, followed by 125 mg b.i.d. for 5 months. Twenty-five male patients with WHO functional class III or 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.

PRECAUTIONS: Hematologic Changes: Treatment with **TRACLEER**® caused a dose-related decrease in hemoglobin and hematocrit. Hemoglobin levels should be monitored after 1 and 3 months of treatment and then every 3 months. 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 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 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. 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.

Pulmonary Veno-Occlusive Disease (PVOD): Should signs of pulmonary edema occur when **TRACLEER**® is administered the possibility of associated PVOD should be considered and **TRACLEER**® should be discontinued.

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 enzymes may increase the plasma concentration of bosentan (see ketoconazole). Concomitant administration of both a CYP2C9 inhibitor (e.g., fluconazole or amiodarone) and a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, ritonavir) or a moderate CYP3A4 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 CYP3A4 inhibitor with **TRACLEER**® is not recommended. Bosentan is an inducer of CYP3A4 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, CYP3A4). Consequently, **TRACLEER**® is not expected to increase the plasma concentrations of drugs metabolized by these enzymes.

Hormonal Contraceptives, Including Oral, Injectable, Transdermal, and Implantable Contraceptives:

An in vitro study demonstrated that co-administration of bosentan and the oral hormonal contraceptive Orthonovum® 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. Therefore, hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when **TRACLEER**® is co-administered. Women should practice additional methods of contraception and not rely on hormonal contraception alone when taking **TRACLEER**®. Specific interaction studies have demonstrated the following: **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. The concomitant administration of bosentan and cyclosporine A is contraindicated (see **CONTRAINDICATIONS**). Co-administration of bosentan decreased the plasma concentrations of cyclosporine A (a CYP3A4 substrate) by approximately 50%.

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. Therefore, the concomitant administration of **TRACLEER**® and glyburide is contraindicated, and alternative hypoglycemic agents should be considered (see **CONTRAINDICATIONS**). 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 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, such as 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 no significant pharmacokinetic interactions with digoxin and nimodipine, and losartan has no significant effect on plasma levels of bosentan.

Sildenafil: In healthy subjects, co-administration of multiple doses of 125 mg b.i.d. bosentan and 80 mg t.i.d. sildenafil resulted in a reduction of sildenafil plasma concentrations by 63% and increased bosentan plasma concentrations by 50%. A dose adjustment of neither drug is necessary. This recommendation holds true when sildenafil is used for the treatment of pulmonary arterial hypertension or erectile dysfunction.

Iloprost: In a small, randomized, double-blind, placebo-controlled study (the STEP trial), 34 patients treated with bosentan 125 mg bid 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.

Rifampicin: Co-administration of bosentan and rifampicin in normal volunteers resulted in a mean 6-fold increase in bosentan trough levels after the first concomitant dose, but about a 60% decrease in bosentan levels at steady-state. The effect of bosentan on rifampicin levels has not been assessed. When consideration of the potential benefits and known and unknown risks leads to concomitant use, measure LFTs weekly for the first 4 weeks before reverting to normal monitoring.

Lopinavir/ritonavir or other ritonavir-containing HIV regimens: Co-administration of **TRACLEER**® and lopinavir/ritonavir in healthy subjects resulted in initial and steady state trough plasma concentrations of bosentan that were approximately 48-fold and 5-fold higher, respectively, than those measured after **TRACLEER**® administered alone. This is most likely explained by inhibition by ritonavir of OATP-mediated uptake into hepatocytes, but the potential for increased toxicity cannot be excluded. Co-administration of bosentan and lopinavir/ritonavir or other ritonavir-containing HIV regimens is contraindicated (see **CONTRAINDICATIONS**).

continued on next page

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 as low as 450 mg/kg/day (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 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of in vitro tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an in vivo mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Impairment of Fertility/Testicular Function: The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents. Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/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).

Pregnancy, Teratogenic Effects: Category X (See **CONTRAINDICATIONS**).

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: Adverse Events: See **BOX WARNING** for discussion of liver injury and **PRECAUTIONS** for discussion of hemoglobin and hematocrit abnormalities. 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. Doses up to 8 times the currently recommended clinical dose (125 mg b.i.d.) were administered for a variety of durations. The exposure to bosentan in these trials ranged from 1 day to 4.1 years (N = 89 for 1 year; N = 61 for 1.5 years and N = 39 for more than 2 years). Exposure of pulmonary arterial hypertension patients (N = 235) to bosentan ranged from 1 day to 1.7 years (N = 126 more than 6 months and N = 28 more than 12 months). Treatment discontinuations due to adverse events other than those related to pulmonary hypertension during the clinical trials in patients with pulmonary arterial hypertension were more frequent on 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. The adverse drug reactions that occurred in ≥ 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 b.i.d. are shown in Table 1:

Table 1. Adverse events* occurring in ≥ 3% of patients treated with bosentan 125-250 mg b.i.d. and more common on bosentan in placebo-controlled studies in pulmonary arterial hypertension

Adverse Event	Bosentan (N = 165)		Placebo (N = 80)	
	No.	%	No.	%
Headache	36	22%	16	20%
Nasopharyngitis	18	11%	6	8%
Flushing	15	9%	4	5%
Hepatic function abnormal	14	8%	2	3%
Edema, lower limb	13	8%	4	5%
Hypotension	11	7%	3	4%
Palpitations	8	5%	1	1%
Dyspepsia	7	4%	0	0%
Edema	7	4%	2	3%
Fatigue	6	4%	1	1%
Pruritus	6	4%	0	0%

*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.

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%).

Post-Marketing Experience: Hypersensitivity, Rash, Thrombocytopenia, Jaundice, Anemia requiring transfusion: There have been several post-marketing reports of angioneurotic edema 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**®. In the post-marketing 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 rare reports of liver failure. The contribution of **TRACLEER**® in these cases could not be excluded (see **BOX WARNING**).

References for previous pages: 1. Data on file, Actelion Pharmaceuticals. 2. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903. 3. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001;358:1119-1123.

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