Product Monograph
Including Patient Medication Information

PrTRACLEER®

Bosentan tablets

For oral use

62.5 mg and 125 mg bosentan (as bosentan monohydrate)

Endothelin Receptor Antagonist

Janssen Inc.*
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Toronto, Ontario
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*a Johnson & Johnson company

Recent Major Label Changes

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Part 1: Healthcare Professional Information

1 Indications

TRACLEER® (bosentan monohydrate) is indicated for the treatment of:

- pulmonary arterial hypertension in patients with WHO functional class III or IV primary pulmonary hypertension, or
- pulmonary hypertension secondary to scleroderma or congenital heart disease or human immunodeficiency virus in patients who did not respond adequately to conventional therapy.

As well, a prolongation of time to clinical worsening was shown in patients with WHO functional class II.

1.1 Pediatrics

Pediatrics (<18 years of age): There is only limited experience with TRACLEER in patients under the age of 18 years (see 7.1.3 Pediatrics). Based on the data submitted and reviewed by Health Canada, the safety and efficacy of TRACLEER in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Data available to Health Canada are insufficient to establish differences in the safety and efficacy associated with the use of TRACLEER in geriatric patients.

2 Contraindications

Bosentan monohydrate is contraindicated in patients:

- who are hypersensitive to bosentan or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, (see 6 Dosage Forms, Strengths, Composition and Packaging.)
- who are pregnant, or of childbearing potential unless adequate contraceptive measures are taken. Fetal malformations were reported in animals (see 7.1.1 Pregnancy).
- with moderate or severe liver impairment and/or with baseline values of liver transaminases, i.e., aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), greater than 3 times the upper limit of normal (ULN), particularly when the total bilirubin is increased to greater than 2 times the ULN (see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).
- with concomitant use of cyclosporine A.
- with concomitant use of glyburide.

4 Dosage and Administration

4.1 Dosing Considerations

Use of TRACLEER in patients with moderate or severe liver impairment is contraindicated (see 2 Contraindications, 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics, Hepatic Insufficiency).

Hemoglobin concentrations management:

Hemoglobin concentrations should be checked prior to the initiation of treatment, after 1 month and after 3 months, and quarterly thereafter. (See 7 Warnings and Precautions, Hematologic).

Liver abnormalities management:
Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals (see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic and Monitoring and Laboratory Tests).

Use with Protease Inhibitors:
Co-administration of bosentan in patients already on protease inhibitors for at least 10 days:
Start at 62.5 mg once daily or every other day based upon individual tolerability.

Co-administration of protease inhibitors/antiretroviral agents in patients on bosentan:

Discontinue use of bosentan at least 36 hours prior to initiation of protease inhibitors. After at least 10 days following the initiation of protease inhibitors, resume bosentan at 62.5 mg once daily or every other day based upon individual tolerability.

4.2 Recommended Dose and Dosage Adjustment

TRACLEER should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the recommended maintenance dose of 125 mg twice daily. Doses above 125 mg twice daily do not confer additional benefit sufficient to offset the increased risk of liver injury.

- **Dosage in Pediatric Patients:** There is only limited experience with TRACLEER in patients under the age of 18 years (see 7.1.3 Pediatrics). Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

- **Dosage in Elderly Patients:** Clinical studies of TRACLEER did not include a sufficient number of patients aged 65 and over to determine if they respond differently than younger patients with pulmonary arterial hypertension. In general, dose selection for an elderly patient should be made cautiously, reflecting a possible decrease in renal and/or cardiac function, concomitant disease, other drug therapy, and, particularly, decrease in hepatic function.

- **Dosage in Patients with Hepatic Impairment:** No dose adjustment of TRACLEER is needed in patients with mild hepatic impairment (i.e., Child-Pugh class A). Use of TRACLEER in patients with moderate or severe liver impairment is contraindicated (see 2 Contraindications, 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic and 10.3 Pharmacokinetics, Hepatic Insufficiency).

- **Dosage in Patients with Renal Impairment:** The effect of renal impairment on the pharmacokinetics of TRACLEER is small. No dosing adjustment is required including patients undergoing dialysis.

Discontinuation of Treatment
There is no experience with abrupt discontinuation of TRACLEER at the recommended doses in pulmonary arterial hypertension patients. However, to avoid the possible occurrence of sudden clinical deterioration as has been seen with the discontinuation of other medications for

this disease, patients should be monitored closely and reducing the dose by half for 3 to 7 days prior to discontinuation should be considered.

4.4 Administration

The film-coated tablets are to be swallowed with water.

TRACLEER should be taken morning and evening, consistently, with or without food.

4.5 Missed Dose

If a scheduled dose of TRACLEER is missed, a double dose should not be taken to make up for the forgotten individual dose. The patient should take the next tablet at the usual scheduled time.

5 Overdose

TRACLEER has been given as a single dose of up to 2,400 mg in normal volunteers, or up to 2,000 mg/day for two months in patients, without any major clinical consequences. The most common side effect was headaches of mild-to-moderate intensity. In the cyclosporine A interaction study, where doses of 500 and 1,000 mg of TRACLEER were given concomitantly with cyclosporine A, initial trough plasma concentrations of TRACLEER increased 30-fold resulting in severe headaches, nausea, and vomiting, but no serious adverse events occurred. Mild decreases in blood pressure and increases in heart rate were observed.

Massive overdosage may result in pronounced hypotension requiring active cardiovascular support. In the post-marketing period there was one reported overdose of 10,000 mg of TRACLEER taken by an adolescent male patient. He had symptoms of nausea, vomiting, hypotension, dizziness, sweating, blurred vision. He recovered completely within 24 hours with blood pressure support. Note: bosentan is not removed through dialysis.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal ingredients
Oral	Tablet, 62.5 mg and 125 mg bosentan (from bosentan monohydrate)	**Tablet contents:** corn starch, glyceryl behenate, magnesium stearate, povidone, pregelatinized starch, and sodium starch glycolate **Film coating:** ethylcellulose, hydroxypropylmethylcellulose, iron oxide red, iron oxide yellow, talc, titanium dioxide and triacetin.

TRACLEER is supplied as follows:

- 62.5 mg film-coated, round, biconvex, orange-white tablets debossed with '62,5' on one side in carton box containing 4 blisters of 14 tablets each (56 tablets in total).
- 125 mg film-coated, oval, biconvex, orange-white tablets debossed with '125' on one side in carton box containing 4 blisters of 14 tablets each (56 tablets in total).

7 Warnings and Precautions

General

Pulmonary veno-occlusive disease

Cases of pulmonary edema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary edema occur when TRACLEER is administered in patients with PAH, the possibility of associated veno-occlusive disease should be considered. In the post-marketing period there have been rare reports of pulmonary edema in patients treated with TRACLEER who had a suspected diagnosis of pulmonary veno-occlusive disease.

Fluid retention

In a placebo-controlled study, 1,611 patients with severe chronic heart failure were treated with TRACLEER for a mean duration of 1.5 years. In this study there was one new safety finding that was not previously observed in the pulmonary arterial hypertension studies. This was an early increased incidence of hospitalization due to worsening of chronic heart failure with no difference in mortality between TRACLEER and placebo-treated patients. At the end of the study, there was no difference in overall hospitalizations for heart failure or in mortality between TRACLEER and placebo-treated patients. This effect was observed during the first 4-8 weeks of treatment with TRACLEER and could have been the result of fluid retention. In this trial, fluid retention was reflected by early weight gain, decreased hemoglobin concentration, and increased incidence of leg edema.

In the placebo-controlled trials with pulmonary arterial hypertension patients, peripheral edema and decreased hemoglobin concentrations were reported with no evidence for increased incidence of early hospitalization due to clinical worsening.

It is recommended that patients be monitored for signs of fluid retention (e.g., leg edema, weight gain). Should this occur, starting treatment with diuretics or increasing the existing dose of diuretics is recommended. Treatment with diuretics is recommended in patients with evidence of fluid retention before the start of treatment with TRACLEER.

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.

Carcinogenesis and Genotoxicity

See 16 Non-Clinical Toxicology.

Cardiovascular

TRACLEER should be initiated with caution if the patient has a systemic systolic blood pressure lower than 85 mm Hg.

Driving and Operating Machinery

No studies on the effect of TRACLEER on the ability to drive and use machines have been performed. TRACLEER can induce hypotension, blurred vision and dizziness that can impact the ability to drive or use machines. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hematologic

Treatment with TRACLEER has been associated with dose-related decreases in hemoglobin concentration (0.9 g/dL overall average), which is likely due to hemodilution. In placebo-controlled studies TRACLEER-related decreases in hemoglobin concentration were not progressive, and stabilized after the first 4-12 weeks of treatment. It is recommended that hemoglobin concentrations be checked prior to the initiation of treatment, after 1 month and after 3 months, and quarterly thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and the need for specific treatment. In the post-marketing period, cases of anemia requiring red blood cell transfusion have been reported (see 8.5 Post-Market Adverse Drug Reactions).

Hepatic/Biliary/Pancreatic

TRACLEER has been associated with a reversible, dose-related increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), accompanied in some cases by elevated bilirubin. Increases in liver enzymes usually occurred within the first 26 weeks following initiation of treatment and returned to pretreatment levels without sequelae within a few days to 9 weeks, either spontaneously or after dose reduction or discontinuation. These increases may also occur late in treatment.

In the post-marketing period, 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. Rare cases of autoimmune hepatitis with a latency of a few months to years have also been reported. 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.

Liver transaminase levels must be measured prior to initiation of treatment and subsequently at monthly intervals.

Pre-existing Liver Impairment:
Use in patients with baseline values of liver transaminases, i.e., aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT), greater than 3 times the upper limit of normal (ULN), particularly when the total bilirubin is increased to greater than 2 times the ULN, is contraindicated (see 2 Contraindications).

Management of Patients with Increased Liver Transaminases:

ALT/AST levels	Treatment and monitoring recommendations are as follows:
> 3 and ≤ 5 x ULN	Confirm by another liver function test; if confirmed, reduce the daily dose or stop treatment, monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pretreatment values consider continuing or reintroducing TRACLEER as appropriate (see Reintroduction of Treatment below).
> 5 and ≤ 8 x ULN	Confirm by another liver function test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. Once the aminotransferase levels return to pretreatment values consider reintroducing TRACLEER (see Reintroduction of Treatment below).
> 8 x ULN	Treatment must be stopped and reintroduction of TRACLEER is not to be considered.

In the case of elevations of aminotransferases accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice or unusual lethargy or fatigue) or of increases in bilirubin ≥2 x ULN, treatment must be stopped and reintroduction of TRACLEER is not to be considered.

Reintroduction of treatment
Reintroduction of treatment with TRACLEER should only be considered if the potential benefits of treatment with TRACLEER outweigh the potential risks and when aminotransferase levels are within pretreatment values. TRACLEER is to be reintroduced at the starting dose and aminotransferase levels must then be checked within 3 days after reintroduction, then again after further 2 weeks, and thereafter according to the recommendations above.

Monitoring and Laboratory Tests

Liver abnormalities management
Liver transaminase levels must be measured prior to initiation of treatment and subsequently at monthly intervals. For liver abnormalities management, see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic.

Hemoglobin concentrations management
Hemoglobin concentrations should be checked prior to the initiation of treatment, after 1 month and after 3 months, and quarterly thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and the need for specific treatment. (See 7 Warnings and Precautions, Hematologic).

Reproductive Health

- **Fertility**

It cannot be excluded that bosentan may have a detrimental effect on spermatogenesis (decrease sperm count) in men. In male children, a long-term impact on fertility after treatment with bosentan cannot be excluded.

7.1 Special Populations

7.1.1 Pregnancy

TRACLEER should be considered a potential human teratogen. TRACLEER has been shown to be teratogenic in rats when given at doses ≥60 mg/kg/day (twice the human oral therapeutic dose of 125 mg b.i.d., on an mg/m^2 basis). In an embryo-fetal toxicity study in rats, TRACLEER showed dose-dependent teratogenic effects including malformations of the head and face and of the major vessels. No birth defects were observed in rabbits at doses of up to 1500 mg/kg/day; however, the plasma concentrations were lower than those reached in rats. The similarity of malformations induced by TRACLEER and those observed in endothelin-1 knockout mice and in animals treated by other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs. There are no studies in pregnant women.

TRACLEER treatment must not be initiated in women of childbearing potential unless they practice reliable contraception and the result of the pretreatment pregnancy test is negative.

Before the initiation of TRACLEER treatment in women of childbearing potential, the absence of pregnancy should be checked, appropriate advice on reliable method of contraception provided, and reliable contraception initiated. Patients and prescribers must be aware that, due to potential pharmacokinetic interactions, TRACLEER may render hormonal contraceptives ineffective (see 9.4 Drug-Drug Interactions). Therefore, women of childbearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but should use an additional or an alternative reliable method of contraception. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynecologist is recommended.

Because of possible hormonal contraception failure during TRACLEER treatment and also bearing in mind the risk that pulmonary hypertension severely deteriorates with pregnancy, monthly pregnancy tests during treatment with TRACLEER are recommended to allow early detection of pregnancy.

7.1.2 Breastfeeding

Data from a case report describe the presence of bosentan in human milk. There is insufficient information about the effects of bosentan on the breastfed infant. Because the adverse reactions (see 7 Warnings and Precautions and 8 Adverse Reactions) associated with the use of TRACLEER could potentially occur in the breastfed infant, breast-feeding is not recommended during treatment with TRACLEER.

7.1.3 Pediatrics

Pediatrics (3-18 years of age): The safety and efficacy of TRACLEER in children was studied in a group of 19 patients ages 3-15 years with PAH either primary or secondary to various congenital heart defects, in WHO functional class II or III. Of the 19 patients, 10 were receiving concomitant FLOLAN (epoprostenol). After 12 weeks of treatment with TRACLEER, efficacy could not be demonstrated based on increased exercise capacity. However, statistically significant improvements in certain hemodynamic indices were noted (mean pulmonary artery pressure, mean systemic artery pressure, pulmonary vascular resistance and pulmonary vascular resistance index, systemic vascular resistance and systemic vascular resistance index, cardiac output and stroke index). No statistically significant improvement in respiratory parameters (oxygen and CO_2) or cardiac index was present. By treatment end, five patients

had improved by one functional class and one deteriorated. No new safety concerns arose during the study, though one patient was withdrawn from treatment due to increased liver transaminases.

The dosing regimen used in the study was based on body-weight with a recommended target dose of 2 mg/kg, morning and evening. There is extremely limited clinical experience in children below 1 year of age.

Body Weight (kg)	Initiation Dose	Maintenance Dose
10 ≤ x ≤ 20	31.25 mg q.d.	31.25 mg b.i.d.
20 ≤ x ≤ 40	31.25 mg b.i.d.	62.5 mg b.i.d.
> 40 kg	62.5 mg b.i.d.	125 mg b.i.d.

Health Canada has not authorized an indication for pediatric use of TRACLEER.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Limited clinical experience with TRACLEER in patients aged 65 years or older has not identified any difference in response between elderly and younger patients, but the possibility of decreased hepatic function in the elderly should be considered (see 4.2 Recommended Dose and Dosage Adjustment).

8 Adverse Reactions

8.1 Adverse Reaction Overview

Safety data on TRACLEER were obtained from placebo-controlled and open-label studies in 677 patients with pulmonary arterial hypertension or other conditions. Doses up to 8 times the currently recommended maintenance dose for pulmonary arterial hypertension were administered. The duration of treatment ranged from 1 day to 4.1 years. In the placebo-controlled studies, the adverse events that occurred more frequently in patients treated with TRACLEER than those treated with placebo were flushing, leg edema, abnormal hepatic function, headache and anemia. Treatment with TRACLEER has been associated with dose-dependent elevations in liver aminotransferases and decreases in hemoglobin concentration.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

In placebo-controlled studies 258 were patients with pulmonary arterial hypertension. They received TRACLEER at doses of 250 mg (n=188) or 500 mg (n=70) per day. At the recommended maintenance dose of 125 mg b.i.d., adverse events that occurred at an incidence greater than 1% in TRACLEER -treated patients with pulmonary arterial hypertension are given in the following table:

Table 1: Incidence of adverse events, regardless of drug causality, occurring in >1% of patients treated with TRACLEER (125 mg b.i.d.) in placebo-controlled studies in pulmonary arterial hypertension

System Organ Class / Adverse Events (AEs)	TRACLEER n=188		Placebo n=172	
	n	(%)	N	(%)
All system Organ Classes				
Total patients with at least one AE	155	(82)	135	(79)
Total number of AEs	504		548	
Blood and lymphatic system disorders				
Anemia	6	(3)		
Cardiac disorders				
Palpitations	6	(3)	3	(2)
Eye disorders				
Vision blurred	3	(2)	2	(1)
Gastrointestinal disorders				
Nausea	15	(8)	19	(11)
Diarrhea	8	(4)	13	(8)
Abdominal pain	5	(3)	7	(4)
Vomiting	4	(2)	10	(6)
Dyspepsia	4	(2)	4	(2)
Abdominal distension	4	(2)	3	(2)
Rectal hemorrhage	4	(2)		
Constipation	3	(2)	4	(2)
Dry mouth	3	(2)	2	(1)
Mouth ulceration	3	(2)		
General disorders and administration site conditions				
Edema peripheral	15	(8)	13	(8)
Chest pain	10	(5)	8	(5)
Edema	5	(3)	4	(2)
Influenza like illness	4	(2)	2	(1)
Infections and infestations				
Nasopharyngitis	16	(9)	14	(8)
Upper respiratory tract infection	15	(8)	11	(6)
Sinusitis	7	(4)	4	(2)
Bronchitis	6	(3)	12	(7)
Urinary tract infection	5	(3)	6	(4)
Respiratory tract infection	5	(3)	5	(3)
Influenza	4	(2)	8	(5)
Lower respiratory tract infection	3	(2)	4	(2)
Pharyngitis	3	(2)	1	(1)
Ear infection	3	(2)		
Injury, poisoning and procedural complications				
Contusion	4	(2)	1	(1)
Investigations				
Liver function test abnormal	8	(4)	3	(2)

System Organ Class / Adverse Events (AEs)	TRACLEER n=188		Placebo n=172	
	n	(%)	N	(%)
Hepatic enzyme increased	3	(2)		
Musculoskeletal and connective tissue disorders				
Back pain	7	(4)	6	(4)
Arthralgia	6	(3)	3	(2)
Muscle spasms	5	(3)	6	(4)
Shoulder pain	4	(2)	4	(2)
Nervous system disorders				
Headache	24	(13)	25	(15)
Dizziness	18	(10)	23	(13)
Syncope	8	(4)	7	(4)
Respiratory, thoracic and mediastinal disorders				
Cough	9	(5)	14	(8)
Pulmonary hypertension	8	(4)	23	(13)
Dyspnea	6	(3)	7	(4)
Epistaxis	6	(3)	7	(4)
Hemoptysis	4	(2)	4	(2)
Dyspnea exacerbated	3	(2)	6	(4)
Dyspnea exertional	3	(2)	1	(1)
Vascular disorders				
Flushing	8	(4)	5	(3)
Hypotension	6	(3)	3	(2)

In placebo-controlled studies of TRACLEER in the treatment of pulmonary arterial hypertension and other diseases, a total of 677 patients were treated with TRACLEER and 288 patients were treated with placebo, with doses ranging from 100 mg to 2,000 mg per day. The duration of treatment ranged from four weeks to six months. Adverse events that occurred at an incidence greater than 1% in TRACLEER-treated patients are given in the following table:

Table 2: Incidence of adverse events, regardless of drug causality, occurring in >1% of patients treated with TRACLEER in placebo-controlled studies

System Organ Class / Adverse Events (AEs)	TRACLEER n=677		Placebo n=288	
	n	(%)	n	(%)
All System Organ Classes				
Total patients with at least one AE	529	(78)	220	(76)
Total number of AEs	1591		840	
Blood and Lymphatic System Disorders				
Anemia (NOS)	23	(3)	3	(1)
Cardiac Disorders				
Angina Pectoris	15	(2)	3	(1)
Cardiac failure	120	(18)	64	(22)
Edema (NOS)	16	(2)	3	(1)
Edema – Legs (Edema lower limb)	32	(5)	4	(1)

System Organ Class / Adverse Events (AEs)	TRACLEER n=677		Placebo n=288	
	n	(%)	n	(%)
Palpitations	18	(3)	5	(2)
Gastrointestinal Disorders				
Abdominal pain (NOS)	13	(2)	11	(4)
Constipation	15	(2)	7	(2)
Diarrhea (NOS)	30	(4)	18	(6)
Dyspepsia	11	(2)	3	(1)
Nausea	31	(5)	30	(10)
Vomiting	16	(2)	12	(4)
General Disorders				
Chest pain (NEC)	27	(4)	20	(7)
Fatigue	14	(2)	12	(4)
Pyrexia	13	(2)	5	(2)
Hepato-biliary Disorders				
Hepatic function abnormal	40	(6)	6	(2)
Infections and Infestations				
Influenza	20	(3)	14	(5)
Metabolic and Nutritional Disorders				
Gout	12	(2)	7	(2)
Musculo-Skeletal, Connective Tissue and Bone Disorders				
Arthralgia	14	(2)	10	(3)
Back pain	17	(3)	8	(3)
Pain in limb	12	(2)	7	(2)
Nervous System Disorders				
Dizziness (exc. Vertigo)	80	(12)	39	(14)
Headache NOS	107	(16)	37	(13)
Vision blurred	20	(3)	7	(2)
Syncope	20	(3)	12	(4)
Respiratory, Thoracic and Mediastinal Disorders				
Bronchitis	19	(3)	10	(3)
Coughing	26	(4)	13	(5)
Dyspnea (NOS)	26	(4)	14	(5)
Nasopharyngitis	23	(3)	10	(3)
Pneumonia	11	(2)	2	(1)
Sinusitis	12	(2)	5	(2)
Lower respiratory tract infection	12	(2)	5	(2)
Upper respiratory tract infection	32	(5)	18	(6)
Renal and Urinary Disorders				
Urinary tract infection	18	(3)	12	(4)
Skin and Subcutaneous Tissue Disorders				
Pruritus (NOS)	12	(2)		
Vascular Disorders				
Epistaxis	12	(2)	5	(2)
Flushing	45	(7)	5	(2)
Hypotension (NOS)	46	(7)	22	(8)
Postural hypotension	13	(2)	14	(5)

NOS= Not otherwise specified
NEC= Not elsewhere classified
Note: The population studied included patients with pulmonary arterial hypertension as well as patients with other conditions. The doses used in some placebo-controlled studies were higher than those recommended for pulmonary arterial hypertension.

Testicular Function
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 and IV PAH and normal baseline sperm count were enrolled; 23 completed the study and 2 discontinued due to adverse events not related to testicular function. 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. The relevance of this observation is uncertain considering the large natural intrasubject variability of sperm counts. Although, based on this finding, it cannot be excluded that endothelin receptor antagonists such as TRACLEER may have an effect on spermatogenesis, the absence of a systematic effect of chronic bosentan treatment on testicular function in humans observed in this study is in line with the toxicology data for bosentan (see 16 Non-Clinical Toxicology).

Combination with Epoprostenol
In study AC-052-355 (BREATHE-2) in adult patients, the most frequent adverse event experienced with the combination was jaw pain (59.1% on TRACLEER + epoprostenol and 90.9% on placebo + epoprostenol), a known side effect of epoprostenol therapy. Among the events associated with TRACLEER therapy, only leg edema was more frequent on TRACLEER plus epoprostenol than placebo plus epoprostenol (27.3% vs 9.1%). Few patients in either group experienced a serious adverse event or had treatment discontinued because of an adverse event. Two patients on combination therapy died during the study from progression of disease, and another died 36 days after having been withdrawn from the study because of a worsening condition. None of the deaths were considered by the investigator to be related to treatment but rather a reflection of the natural progression of the disease.

Incidences of elevated liver aminotransferases to clinically relevant values were higher on placebo plus epoprostenol (18.2%) than on TRACLEER plus epoprostenol therapy (9.5%). Similarly, the incidences of clinically relevant decreases in hemoglobin were higher on placebo plus epoprostenol (10.0%) than on TRACLEER plus epoprostenol therapy (0%). The clinical pattern of laboratory abnormalities in the TRACLEER plus epoprostenol group was consistent with previous findings. No meaningful changes in ECG parameters were seen in either group, and no change in pulse rate was observed with TRACLEER plus epoprostenol. Decreases in blood pressures were observed in both groups, but the decrease in systolic blood pressure was smaller in the group on combination therapy than on placebo plus epoprostenol. No cases of hypotension or postural hypotension were reported on the combination therapy.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

In a study in children and adolescents, 17 of the 19 patients (89.5%) reported at least one adverse event. The most frequent adverse events were flushing (four patients), headache, and

abnormal hepatic function (three patients each). Dizziness, fluid retention, aggravated PAH, pyrexia, and a variety of infections (including respiratory) occurred in two patients each.

Flushing was noted only in patients also on epoprostenol. Mild fluid retention was reported for two patients and moderate edema for one, but unlike most cases in previous studies did not occur early in treatment, but rather after at least 79 days of treatment. The incidences of these and other adverse events did not appear to have any relationship to weight group.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Blood and Lymphatic System Disorders: ecchymosis, thrombocytopenia

Cardiac Disorders: complete atrioventricular block, cardiac arrest, myocardial infarction, tachycardia, ventricular arrhythmia, ventricular tachycardia

Eye Disorders: conjunctivitis, eye inflammation, photophobia, xerophthalmia

Gastrointestinal Disorders: anorexia, ascites, duodenal ulcer, flatulence, gastroenteritis, mouth ulceration, intestinal obstruction, loose stools

General Disorders: chest pain (non cardiac), feeling hot, lethargy, pain, shivering, thirst, weakness

Immune System Disorders: anaphylactic shock, urticaria

Infections and Infestations: infection

Investigations: blood alkaline phosphatase increased, blood lactate dehydrogenase increased, decreased weight, hyperglycemia, hypoglycemia, increased blood urea, increased eosinophil count, prolonged coagulation time, shortened coagulation time

Metabolism and Nutrition Disorders: dehydration, hypokalemia, hyponatremia, impaired glucose tolerance

Musculoskeletal Disorders: gout, muscle cramps, muscle twitching, musculoskeletal pain, sensation of heaviness

Nervous System Disorders: central nervous system depression, cerebrovascular accident, hemiparesis, hydrocephalus, hypoesthesia, insomnia, paresthesia, somnolence, tinnitus, tremor, vasovagal attack, vertigo

Psychiatric Disorders: anxiety, disturbance in attention, irritability, increased libido, mood swings, nightmares, panic attack

Respiratory, Thoracic and Mediastinal Disorders: aspiration, asthma, bronchospasm, hemoptysis, pneumonia, respiratory depression, respiratory failure, increased sputum

Skin and Subcutaneous Tissue Disorders: dermatitis, dry skin, eczema, erythema multiforme, erythema, skin discoloration, Stevens-Johnson syndrome, increased sweating

Renal Disorders: cystitis, dysuria, hematuria, renal failure, renal impairment, urinary frequency, urine discoloration

Vascular Disorders: epistaxis, hypertension, peripheral ischemia, subarachnoid hemorrhage, restless leg syndrome

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

In placebo-controlled studies, increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to more than three times the upper limit of normal (ULN) were observed in 11% of TRACLEER-treated patients (n=658) as compared to 2% of placebo-treated patients (n=280). Increase in aminotransferases equal or greater than 3 times of ULN was seen in 12.4% of 188 patients with pulmonary arterial hypertension treated with 125 mg b.i.d. and 14% of 70 patients with pulmonary arterial hypertension treated with 250 mg b.i.d. Increase in aminotransferases equal or greater than 8 times of ULN was seen in 3.8% of patients with pulmonary arterial hypertension on 125 mg b.i.d. and 7% of patients with pulmonary arterial hypertension on 250 mg b.i.d. Increases in bilirubin to more than three times the upper limit of normal were associated with aminotransferase increases in 2 of 658 (0.3%) of patients treated with TRACLEER.

Elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) associated with TRACLEER are dose-dependent, occur most often early but occasionally 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. In the post-marketing period, rare cases of liver cirrhosis and liver failure have been reported (see 8.5 Post-Market Adverse Reactions and 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic).

In the placebo-controlled trials of all uses of TRACLEER, marked decreases in hemoglobin (>15% decrease from baseline and <11 g/dL) were observed in 6.2% of TRACLEER-treated patients as compared to 2.9% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 mg and 250 mg b.i.d., marked decreases in hemoglobin occurred in 4.3% of patients compared to 1.2% in placebo-treated patients.

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

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

In the post-marketing period, cases of anemia requiring red blood cell transfusion have been reported (see 8.5 Post-Market Adverse Reactions).

It is recommended that hemoglobin concentrations be checked after 1 month and after 3 months of treatment and every 3 months thereafter.

8.5 Post-Market Adverse Reactions

Based on an exposure of about 147,000 patients to TRACLEER in the post-marketing period, the majority of adverse events have been similar to those reported in clinical trials.

Undesirable effects are ranked under headings of frequency using the following convention:

- very common: ≥1/10
- common: >1/100, <1/10
- uncommon: >1/1,000, ≤1/100
- rare: >1/10,000, ≤1/1,000
- very rare: ≤1/10,000

Blood and lymphatic system disorders:
Common: anemia or hemoglobin decreases, sometimes requiring red blood cell transfusion (see 7 Warnings and Precautions, Hematologic)
Uncommon: thrombocytopenia
Rare: neutropenia, leucopenia

Gastrointestinal disorders:
Common: nausea
Uncommon: vomiting, abdominal pain, diarrhea

Hepato-biliary disorders:
Uncommon: aminotransferase elevations associated with hepatitis and/or jaundice
Rare: hepatic cirrhosis and liver failure, autoimmune hepatitis
(see 7 Warnings and Precautions, Hepatic/Biliary/Pancreatic)

Immune system disorders:
Rare: anaphylaxis and/or angioedema

Respiratory, thoracic and mediastinal disorders:
Common: nasal congestion

Skin and subcutaneous tissue disorders:
Uncommon: hypersensitivity reaction including dermatitis pruritus and rash

9 Drug Interactions

9.1 Serious Drug Interactions

- Concomitant treatment with glyburide (see 2 Contraindications and 9.4 Drug-Drug Interactions)
- Concomitant treatment with cyclosporine A (see 2 Contraindications and 9.4 Drug-Drug Interactions)

9.2 Drug Interactions Overview

Cytochrome P450 System: Bosentan is a substrate of CYP2C9 and CYP3A4. Concomitant administration of both a CYP2C9 inhibitor (such as fluconazole or voriconazole) and a CYP3A4 inhibitor (such as ketoconazole, itraconazole or ritonavir) with bosentan may theoretically lead to large increases in plasma concentrations of bosentan. Co-administration of such combinations of a potent CYP2C9 inhibitor plus a CYP3A4 inhibitor with TRACLEER is not recommended.

Bosentan is a moderate inducer of CYP3A4 and CYP2C9 and possibly CYP2C19. Consequently, plasma concentrations of drugs metabolized by these two isoenzymes may be decreased when TRACLEER is co-administered. The possibility of altered efficacy of drugs metabolized by these isoenzymes should be considered. The dosage of these products may

need to be adjusted after initiation, dose change or discontinuation of concomitant TRACLEER treatment.

Bosentan had no relevant inhibitory effect on cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Consequently, TRACLEER is not expected to increase plasma concentrations of drugs metabolized by these enzymes.

9.3 Drug-Behaviour Interactions

The interaction of TRACLEER with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3: Drug-Drug Interactions

Co-administered drug	Source of Evidence	Effect	Clinical Comments
Cyclosporine A	CT	Co-administration of TRACLEER ↓ the blood concentrations of cyclosporine A by approximately 50%. This is most likely due to induction of CYP3A4 by TRACLEER. Co-administration of Cyclosporine A with TRACLEER 500 mg BID, ↑ initial trough concentrations of TRACLEER approximately 30-fold compared to those measured after TRACLEER alone. At steady state, TRACLEER plasma concentrations ↑ 3- to 4-fold. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine.	The concomitant administration of TRACLEER and cyclosporine A is contraindicated (see 2 Contraindications).
CYP3A4 inducers, e.g. carbamazepine, phenobarbital, phenytoin and St John's wort	T	Data not available but their concomitant administration is expected to lead to reduced systemic exposure to bosentan.	A clinically significant reduction of TRACLEER efficacy cannot be excluded.

Digoxin	CT	No pharmacokinetic interactions	
Epoprostenol	CT	Data obtained in a study in pediatric PAH patients show that after both single- and multiple-dose administration, the C_{max} and AUC values of bosentan were similar in patients with or without continuous infusion of epoprostenol.	See 14 Clinical Trials.
Glyburide	CT	↓ plasma concentrations of glyburide by approximately 40% ↓ plasma concentrations of TRACLEER by approximately 30%	An increased risk of elevated transaminases 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 2 Contraindications).
Hormonal contraceptives	T	↓in plasma concentration of contraceptive steroids that have significant metabolism by CYP3A4	Hormone-based contraceptives alone, regardless of the route of administration (i.e., oral, injectable, transdermal, and implantable forms), are not considered as reliable methods of contraception (see 7.1.1 Pregnancy) when co-administered with TRACLEER.
Ketoconazole	CT	↑ TRACLEER plasma concentration approximately 2-fold	No dose adjustment of TRACLEER is necessary. However, increased effects of TRACLEER should be considered.
Lopinavir + Ritonavir (and other ritonavir-boosted protease inhibitors)	CT	Co-administration of TRACLEER 125 mg BID and lopinavir + ritonavir 400 +100 mg BID during 9.5 days in healthy volunteers, resulted in initial trough bosentan plasma concentrations: • On day 3-4 were approximately 48-fold ↑ than those measured after TRACLEER administered alone.	In patients receiving lopinavir + ritonavir or other ritonavir-boosted protease inhibitors, TRACLEER should be initiated at a dose of 62.5 mg once daily. Patient's tolerability of TRACLEER should be closely monitored to the

		• On day 9, plasma concentrations of bosentan were approximately 5-fold ↑ than with TRACLEER administered alone. Inhibition by ritonavir of transport protein mediated uptake into hepatocytes and of CYP3A4, thereby reducing the clearance of bosentan, most likely causes this interaction. After co-administration of TRACLEER for 9.5 days, the plasma exposures to lopinavir and ritonavir decreased to a clinically non-significant extent (by approximately 14% and 17%, respectively). However, full induction by bosentan might not have been reached and further decrease of protease inhibitors cannot be excluded.	risk of hypotension and to liver function tests, especially at the beginning of the TRACLEER initiation phase and during titration to the maintenance dose of 125 mg BID. Appropriate monitoring of the HIV therapy is recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors.
Losartan	CT	No effect on plasma levels of TRACLEER	
Nevirapine	T		Due to a marked hepatotoxicity of nevirapine that could increase bosentan liver toxicity, this combination is not recommended.
Nimodipine	CT	No pharmacokinetic interactions	
Norethindrone + ethinyl estradiol	CT	Co-administration of TRACLEER with norethindrone + ethinyl estradiol ↓ plasma concentration of norethindrone by 14% and ethinyl estradiol by 31%. Exposure ↓ as much as 66% and 56% respectively in individual subjects.	Hormonal based contraceptives alone are not considered as reliable method of contraception (see 7.1.1 Pregnancy) when administered with TRACLEER.
Oral hypoglycemic agents predominantly metabolized by CYP2C9 or CYP3A4	T	↓ plasma concentrations of oral hypoglycemic agents	The possibility of worsened glucose control in patients using these agents should be considered.
Rifampicin (rifampin)	CT	Co-administration of TRACLEER 125 mg BID for 7 days and	A significantly reduced effect of bosentan is

		rifampicin, a potent inducer of CYP2C9 and CYP3A4, ↓ the plasma concentrations of bosentan by 58%, and this ↓ reached almost 90% in an individual case.	expected when it is co-administered with rifampicin.
Sildenafil	CT	In healthy volunteers, co-administration of TRACLEER 125 mg BID (steady state) with sildenafil 80 mg three times a day (steady state) resulted in a 63% ↓of the sildenafil AUC and a 50% ↑ of the bosentan AUC. The combination was well tolerated.	No dose adjustment of either drug is considered necessary.
Simvastatin and other statins that have significant metabolism by CYP3A4	CT	Co-administration ↓ plasma concentrations of simvastatin, and of its active ß-hydroxy acid metabolite, by approximately 50%. The plasma concentrations of TRACLEER were not affected.	The possibility of reduced efficacy of these statins should be considered. Monitoring of cholesterol levels and subsequent dosage adjustment should be considered.
Sirolimus	T	No drug-interaction study was performed with sirolimus but co-administration may result in ↑ plasma concentrations of TRACLEER, analogous to co-administration with cyclosporine A. Concomitant TRACLEER may reduce the plasma concentrations of sirolimus.	Concomitant use of TRACLEER and sirolimus is not advisable. Patients in need of the combination should be closely monitored for adverse events related to TRACLEER and for sirolimus blood concentrations.
Tacrolimus	T	No drug-interaction study was performed with tacrolimus but co-administration may result in ↑ plasma concentrations of TRACLEER, analogous to co-administration with cyclosporine A. Concomitant TRACLEER may reduce the plasma concentrations of tacrolimus.	Concomitant use of TRACLEER and tacrolimus is not advisable. Patients in need of the combination should be closely monitored for adverse events related to TRACLEER and for tacrolimus blood concentrations.
Tadalafil	CT	TRACLEER 125 mg twice daily ↓ tadalafil (40 mg once a day) systemic exposure by 42% and C_{max} by 27% following multiple dose co-administration.	

		Tadalafil did not affect the exposure (AUC and C_{max}) of bosentan or its metabolites.	
Warfarin	CT	In patients with pulmonary arterial hypertension, TRACLEER 125 mg BID had no clinically significant effect on prothrombin time/INR when administered to patients receiving chronic warfarin therapy. TRACLEER 500 mg BID↓ plasma concentrations of both S-warfarin and R-warfarin by approximately 30%.	No additional dose adjustment should be needed for warfarin, but routine INR monitoring is recommended.

BID= twice a day; T= Theoretical; CT = Clinical Trial.

9.5 Drug-Food Interactions

Co-administration of TRACLEER with food results in small clinically irrelevant increases in C_{max} (22%) and AUC (10%). Bosentan can be given with or without food.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.
Data on interaction with St John's wort (CYP3A4 inducer) is lacking but concomitant administration is expected to lead to reduced systemic exposure to bosentan. A clinically significant reduction of TRACLEER efficacy cannot be excluded.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

10 Clinical Pharmacology

10.1 Mechanism of Action

Bosentan is a dual endothelin receptor antagonist with affinity for both ET_A and ET_B receptors. Bosentan decreases both pulmonary and systemic vascular resistance, resulting in increased cardiac output without increasing heart rate.

The neurohormone endothelin is a potent vasoconstrictor with the ability to promote fibrosis, cell proliferation, and tissue remodeling. Endothelin concentrations in plasma and tissues are increased in a number of cardiovascular disorders, including pulmonary hypertension, suggesting a pathological role for endothelin in these diseases. In pulmonary arterial hypertension, endothelin plasma concentrations strongly correlate with poor prognosis.

Bosentan is specific for endothelin receptors. Bosentan competes with the binding of endothelin for both ET_A and ET_B receptors with a slightly higher affinity for ET_A receptors. In animal models of pulmonary hypertension, chronic oral administration of bosentan reduced pulmonary vascular resistance and reversed pulmonary vascular and right ventricular hypertrophy. In an animal model of pulmonary fibrosis, bosentan reduced collagen deposition.

10.2 Pharmacodynamics

The clinical pharmacology program for bosentan included 23 studies of <14 days duration, involving 350 healthy subjects and 221 patients, with a total of 434 individuals receiving bosentan.

In healthy subjects, oral administration of bosentan has no clinically relevant effect on heart rate and blood pressure in single and multiple-dose studies at doses up to 1,000 mg.

Plasma endothelin levels increase in a dose- and concentration-dependent manner after i.v. and oral doses of bosentan are administered in healthy subjects. No consistent changes in the plasma levels of other hormonal parameters are found. In these subjects, dose-related headaches of mostly mild-to-moderate intensity are the most frequent adverse event.

In patients with primary pulmonary arterial hypertension and pulmonary arterial hypertension secondary to scleroderma or human immunodeficiency virus, oral bosentan significantly decreases pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), right atrial pressure (RAP), and pulmonary capillary wedge pressure (PCWP) and significantly increases cardiac index (CI) as compared to placebo.

***In vivo* Animal Studies**

Bosentan has an effect not only on hemodynamic variables but also on structural changes and disease progression in rat models of pulmonary hypertension.

In chronic hypoxia and monocrotaline rat models, bosentan at doses of 100 mg/kg/day for up to four weeks decreases pulmonary vascular resistance and reverses pulmonary vascular and right ventricular hypertrophy.

In a rat model of bleomycin-induced pulmonary fibrosis, bosentan at doses of 100 mg/kg/day for up to four weeks decreases pulmonary interstitial fibrosis by reducing collagen deposition in the lungs.

In acute pulmonary hypertension pig models, i.v. administration of bosentan at doses of 3 mg/kg-10 mg/kg prevents acute pulmonary hypertension.

10.3 Pharmacokinetics

The pharmacokinetics of bosentan have mainly been documented in healthy subjects. Limited data in patients show that the exposure to bosentan in adult pulmonary arterial hypertension patients is approximately 2-fold greater than in healthy adult subjects.

Table 4: Summary of bosentan's pharmacokinetic parameters in patients with pulmonary arterial hypertension

	C_{max}	$t_{½}$	AUC_{0-4}
14 days (125 mg twice a day)	2286 ng/ml (1234, 3337)	2.3 hr (1.0 - 6.0)	8912 ng·hr/ml (6296, 11531)

Data are expressed as arithmetic mean (and 95% confidence limits) or, for $t_{1/2}$, as median (and range). Data were obtained from PAH patients treated for at least two weeks with the maintenance dose of 125 mg b.i.d.

In healthy subjects, bosentan displays dose- and time-dependent pharmacokinetics. Clearance and volume of distribution decrease with increased intravenous doses and increase with time. After oral administration, the systemic exposure is proportional to dose up to 500 mg. At higher oral doses C_{max} and AUC increase less than proportionally to the dose.

Upon multiple dosing, plasma concentrations of bosentan decrease gradually to 50%-65% of those seen after single dose administration. This decrease is probably due to auto-induction of metabolizing liver enzymes. Steady-state conditions are reached within 3-5 days.

Absorption

The absolute bioavailability of bosentan is approximately 50% and is unaffected by food. Maximum plasma concentrations are attained within 3-5 hours after oral administration. Pharmacokinetic data following both oral and intravenous administration in adult patients with pulmonary arterial hypertension have been obtained. The data show that the exposure to bosentan in adult pulmonary arterial hypertension patients is about 2-fold greater than in healthy adult subjects.

Distribution

The volume of distribution is about 18 L and the clearance is about 8 L/h. Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Metabolism

Bosentan is metabolized in the liver by the cytochrome P_{450} isoenzymes, CYP3A4 and CYP2C9. Three metabolites of bosentan were identified in human plasma. Only one metabolite, Ro 48-5033, is pharmacologically active. In adult patients, the exposure to this active metabolite is greater than in healthy subjects and it may contribute up to 25% to the effect of bosentan. In patients with evidence of the presence of cholestasis, the exposure to the active metabolite may be increased.

Elimination

Bosentan is eliminated by biliary excretion. The apparent elimination half-life ($t_{1/2}$) is 5.4 hours.

Based on the available data it is not expected that the pharmacokinetics of bosentan will be influenced by gender, body weight, race, or age in the adult population to any relevant extent.

Special populations and conditions

- **Pediatrics**

  The pharmacokinetics of single and multiple oral doses of bosentan have been studied in pediatric patients with pulmonary arterial hypertension (see 7.1.3 Pediatrics). The exposure to bosentan decreased with time in a manner consistent with the known auto-induction properties of bosentan. The mean AUC (CV%) values of bosentan in pediatric patients treated with 31.25, 62.5 or 125 mg b.i.d. were 3496 (49), 5428 (79), and 6124 (27) ng·h/ml, respectively, and were lower than the value of 8149 (47) ng·h/ml observed in adult patients receiving 125 mg b.i.d. No kinetic data are available in children under 3 years. Health Canada has not authorized an indication for pediatric use of TRACLEER.

- **Geriatrics**

  The pharmacokinetics of bosentan have not been evaluated in patients over the age of 65

years.

- **Sex**

  No significant relationship or trend was noted between bosentan pharmacokinetic parameters and gender.

- **Ethnic origin**

  The pharmacokinetics of bosentan were compared between Caucasian and Japanese subjects both after single- and multiple-dose administration. The bosentan pharmacokinetics were similar and dose-proportional in Caucasian and Japanese subjects. Other ethnic differences in bosentan pharmacokinetics have not been evaluated.

- **Hepatic Insufficiency**

  In patients with mildly impaired liver function (Child-Pugh class A) no relevant changes in the pharmacokinetics have been observed and no dose adjustment is required in these patients. The steady-state AUC of bosentan was 9% greater and the AUC of the major metabolite, Ro 48-5033, was 33% greater in patients with mild hepatic impairment than in healthy volunteers. The pharmacokinetics of bosentan have not been studied in patients with Child-Pugh class B or C hepatic impairment and bosentan is contraindicated in this patient population (see 2 Contraindications and 7 Warnings and Precautions, **Hepatic/Biliary/Pancreatic**).

- **Renal Insufficiency**

  In patients with severe renal impairment (creatinine clearance 15-30 ml/min), plasma concentrations of bosentan decreased by approximately 10%, and plasma concentrations of the three metabolites increased about 2-fold as compared to volunteers with normal renal function. No dose adjustment is required in patients with renal impairment, as less than 3% of an administered dose is excreted in urine. The degree to which bosentan is removed by hemodialysis has not been established.

11 Storage, Stability, and Disposal

TRACLEER should be stored at room temperature between 15ºC and 25ºC.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

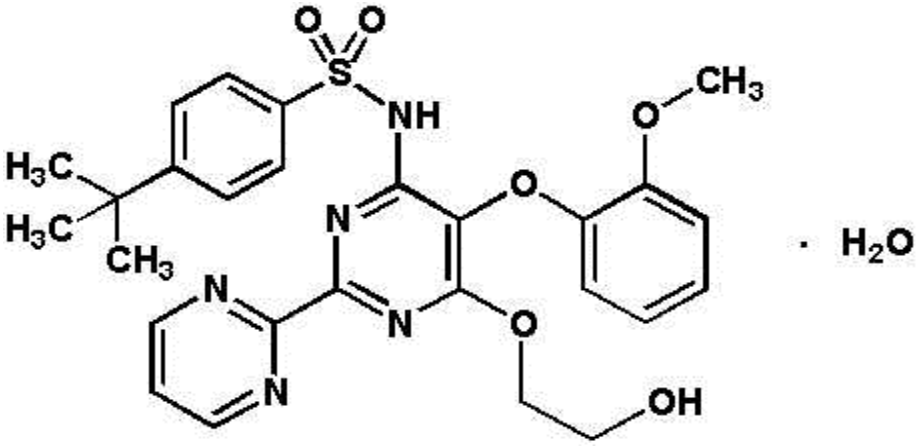
Non-proprietary name of the drug substance(s): Bosentan monohydrate

Chemical name: TRACLEER® (bosentan monohydrate) belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. Its chemical designation is 4-tert-butyl-N - [6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2'] bipyrimidin-4-yl] - benzenesulfonamide monohydrate.

Molecular formula: $C_{27}H_{29}N_5O_6S \cdot H_2O$

Molecular weight: 569.64

Structural formula:



Physicochemical properties: Bosentan monohydrate is a white to yellowish powder.

Solubility: It is poorly soluble in water (1 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.

14 Clinical Trials

14.1 Clinical Trials by Indication

Pulmonary arterial hypertension
Treatment of pulmonary arterial hypertension in patients with WHO functional class III or IV primary pulmonary hypertension, or pulmonary hypertension secondary to scleroderma or congenital heart disease or human immunodeficiency virus in patients who did not respond adequately to conventional therapy.

Table 5: Summary of Patient Demographics for Clinical Trials in Pulmonary Arterial Hypertension

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
AC-052-351	Randomized, double-blind, placebo-controlled	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 8 weeks.	Placebo n=11 Bosentan n=21	Placebo: 47.4 (25-67) Bosentan: 52.2 (33-73)	Placebo: 0M; 11F Bosentan: 4M; 17F
AC-052-352	Randomized, double-blind, placebo-controlled	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to either 125 mg b.i.d., oral, or 250 mg b.i.d., oral, for 12 weeks.	Placebo n=69 Bosentan n=144	Placebo: 47.2 (12-80) Bosentan: 48.7 (13-80)	Placebo: 15M; 54F Bosentan: 30M; 114F
AC-052-353	Open-label, single-arm extension of AC-052-351	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral. Duration: 706 ± 146 days.	N=29	50.2 (26-74)	4M 25F
AC-052-354	Open-label, single-arm extension of AC-052-352	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral. Duration: 479 ± 164 days	n=200	48.5 (13-81)	42M 158F
AC-052-364	Randomized, double-blind, placebo-controlled	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral for 5 months.	Placebo n=92 Bosentan n=93	Placebo: 44.2 (19-79) Bosentan: 45.2 (15-85)	Placebo: 34M; 58F Bosentan: 22M; 71F
AC-052-405	Randomized, double-blind, placebo-controlled Patients with PAH/CHD	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 12 weeks.	Placebo n=17 Bosentan n=37	Placebo: 44.2 (30-56) Bosentan: 37.2 (15-73)	Placebo: 7M; 10F Bosentan: 14M; 23F
AC-052-362	Open-label, non-comparative Patients with PAH/HIV	Starting dose: 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 12 weeks.	N=16	39.2 (29-61)	9M 7F
AC-052-	Randomized,	**Bosentan:**	Placebo	Placebo:	Placebo:

355	double-blind, placebo-controlled, combination therapy bosentan + epoprostenol	starting dose at 62.5 mg b.i.d., oral, for 4 weeks. Up-titrated to 125 mg b.i.d., oral, for 12 weeks. **Epoprostenol:** initiated at 2 ng/kg/min, i.v., 4 days up to 4 ng/kg/min, i.v. Up-titrated by 2 ng/kg/min, i.v., each 2 weeks. Target dose of 12 to 16 ng/kg/min, i.v., by weeks 14 and 16.	n=11 Bosentan n=22	46.6 (15-68) Bosentan: 44.8 (16-69)	5M; 6F Bosentan: 5M; 17F

Study AC-052-351 and Study AC-052-352

Two randomized, double-blind, multi-center, placebo-controlled trials were conducted in 32 (Study AC-052-351) and 213 patients (Study AC-052-352 – BREATHE-1) respectively, with WHO functional class III or IV primary pulmonary hypertension (PPH) or pulmonary arterial hypertension secondary to scleroderma or other connective tissue diseases. The BREATHE-1 study compared 2 doses (125 mg b.i.d. and 250 mg b.i.d.) of TRACLEER with placebo. Study AC-052-351 compared 125 mg b.i.d. with placebo.

In both studies, TRACLEER or placebo was added to patients' existing therapy (oral vasodilators, anticoagulants, diuretics, cardiac glycosides and/or supplemental oxygen, but not epoprostenol). Patients received TRACLEER 62.5 mg or matching placebo twice daily for 4 weeks and then TRACLEER 125 mg or 250 mg b.i.d. or matching placebo twice daily for either 8 (Study AC-052-351) or 12 (BREATHE-1) 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 AC-052-351.

At week 12 (study AC-052-351) or week 16 (BREATHE-1) the main evaluations were performed, and patients were followed for up to 28 weeks. In both trials, treatment with TRACLEER was associated with a significant increase in walking distance. The placebo-corrected increases in the primary efficacy parameter, distance in the 6-minute walk test, compared to baseline were 75.9 ± 31.0 m (95% CL=12.5, 139.2; t-test, p=0.0205) and 44.2 ± 11.6 (95% CL=21.4, 67.0; Mann-Whitney U-test, p=0.0002). The improvement in walk distance was apparent after 1 month of treatment (with 62.5 mg b.i.d.) and fully developed by about 2 months of treatment. It was maintained for up to 7 months of double-blind treatment. (see 4 Dosage and Administration)

Invasive hemodynamic parameters were assessed in Study AC-052-351. As compared to placebo significant improvement from baseline to week 12 was observed with TRACLEER in pulmonary arterial pressure (PAP), cardiac index (CI), pulmonary vascular resistance (PVR), right atrial pressure (RAP) and pulmonary capillary wedge pressure (PCWP).

Table 6: Change from baseline to week 12 in hemodynamic parameters in study AC-052-351

	Baseline		Absolute Change		Treatment Difference
	Tracleer	**Placebo**	**Tracleer**	**Placebo**	
Mean PAP (mm Hg)	n=20 53.7 ± 13.4	n=10 55.7 ± 10.5	n=20 -1.6 ± 5.1	n=10 5.1 ± 8.8	-6.7[1]
Cardiac index (L/min/m^2)	n=20 2.35 ± 0.73	n=10 2.48 ± 10.33	n=20 0.50 ± 0.46	n=10 -0.52 ± 0.48	1.02[2]
PVR (dyn·sec/cm^{-5})	n=19 896 ± 425	n=10 942 ± 430	n=19 -223 ± 245	n=10 191 ± 235	-415[2]
Mean RAP (mm Hg)	n=19 9.7 ± 5.6	n=10 9.9 ± 4.13	n=19 -1.3 ± 4.1	n=10 4.9 ± 4.6	-6.2[2]
PCWP (mm Hg)	n=19 9.3 ± 2.4	n=10 8.3 ± 3.4	n=19 0.1 ± 3.6	n=10 3.9 ± 5.6	-3.8[1]

Values are mean ± SD

1. p<0.05
2. p<0.001

Symptoms of pulmonary arterial hypertension were assessed by WHO functional class, Borg dyspnea score and rate of “clinical worsening”. There was a reduction in dyspnea during walk test (Borg dyspnea score), an improvement in WHO functional class and a significant reduction in the rate of clinical worsening in TRACLEER-treated patients.

In study AC-052-351, 9 patients (42.8%) treated with TRACLEER, had their WHO functional class of pulmonary hypertension improved from class III to class II. In the placebo group, 1 patient (9.1%) improved from class III to class II, and 2 patients (18.1%) deteriorated from class III to class IV. In trial AC-052-352 (BREATHE-1) 92% of the 213 patients were classified at baseline as WHO functional class III and 8% as class IV. Treatment with TRACLEER led to a WHO functional class improvement in 42.4% of patients (placebo 30.4%).

Clinical worsening was assessed as the time to death or hospitalizations for PAH or discontinuation of therapy because of PAH or need for epoprostenol. Figure 1 below shows the Log-rank test reflecting clinical worsening over 28 weeks and the incidences of each component of the clinical worsening endpoint are described in Table 7 below.

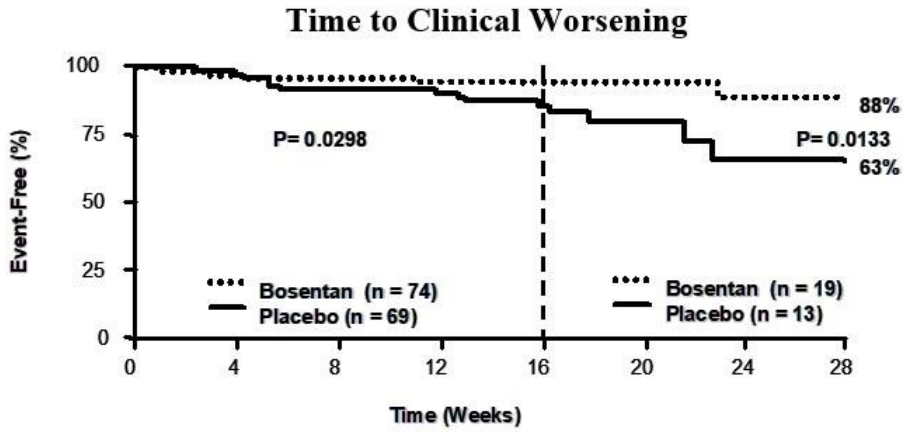
Table 7: Incidence of Clinical Worsening[1]

	BREATHE-1		Study AC-052-351	
	Bosentan 125 mg b.i.d. (n=74)	Placebo (n=69)	Bosentan 125 mg b.i.d. (n=21)	Placebo (n=11)
Patients with clinical worsening [n (%)]	5 (7%)[2]	14 (20%)	0 (0%)[3]	3 (27%)
Death	1 (1%)	2 (3%)	0 (0%)	0 (0%)
Hospitalization for PAH	3 (4%)	9 (13%)	0 (0%)	3 (27%)

Discontinuation due to Worsening of PAH	3 (4%)	6 (9%)	0 (0%)	3 (27%)
Receipt of epoprostenol[4]	2 (3%)	3 (4%)	0 (0%)	3 (27%)

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

1. Shortest time to death, premature withdrawal or hospitalization due to PHT worsening, or initiation of epoprostenol therapy
2. p=0.015 vs placebo by log rank test.
3. p=0.033 vs placebo by Fisher's exact test.
4. 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=74 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=19 in the bosentan group and 13 in the placebo group) continued double-blind therapy for up to 28 weeks.

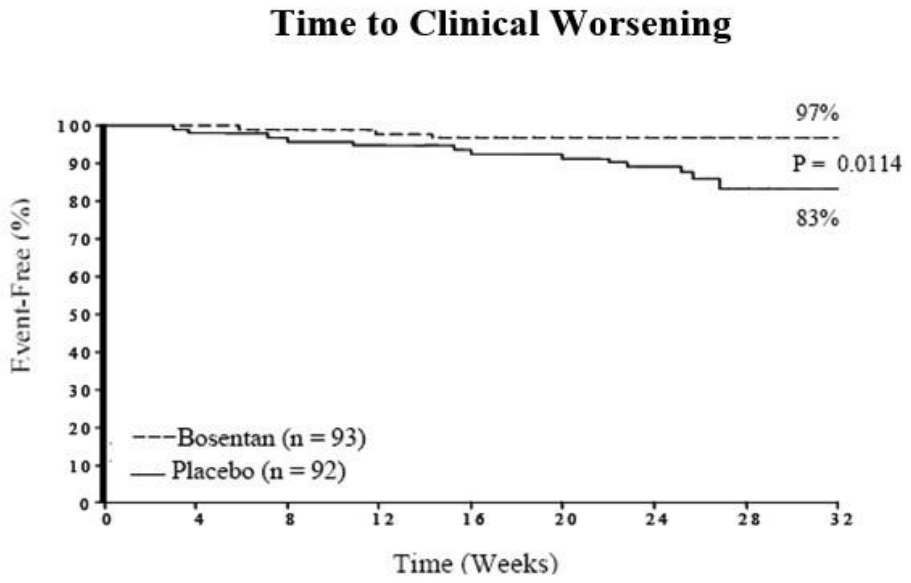
Figure 1: Time from randomization to clinical worsening up to Week 28 in BREATHE-1 Study

Study AC-052-364

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 b.i.d. for 4 weeks followed by 125 mg b.i.d. (n=93), or placebo (n=92) for 5 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 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.

After 6 months of treatment, there was a 22.6% reduction in PVR compared with placebo (p<0.0001). The increase in 6-minute walk distance with bosentan and decrease with placebo resulted in +19.1 meter and +13.8 meter mean and median treatment effects, respectively. The effect did not reach statistical significance (p=0.0758 for median treatment effect). 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 0.227, p=0.0114). Compared with

placebo, bosentan treatment was also associated with a reduced incidence of worsening of at least one functional class (3.4% bosentan vs 13.2% placebo, p=0.0285), and statistically significant improvement in hemodynamic variables (mPAP, TPR, cardiac index, and SVO2; p<0.05). Findings were consistent in strata with or without treatment with sildenafil at baseline.



Time from randomization to clinical worsening with Kaplan-Meier estimate in EARLY.

Figure 2 - Time from randomization to clinical worsening up to Week 32 in EARLY study (AC-052-364).

Study AC-052-353 (Open-label extension of Study AC-052-351) and Study AC-052-354 (Open-label extension of AC-052-352)

Long-term treatment
The long-term effect of TRACLEER was further assessed in two open-label studies (open-label extensions of study AC-052-351 and AC-052-352) with 229 patients treated with TRACLEER for up to 2.5 years with a mean treatment duration of 1.9 ± 0.7 years. During this period, the effects of TRACLEER were maintained in the patients previously treated with TRACLEER. Treatment with TRACLEER in those patients previously on placebo, resulted in an improvement in exercise capacity. Improvement in functional class observed in the initial period of the study tended to decline later.

Long-term survival
Long-term survival was recorded for all 235 patients who were treated with TRACLEER in the two pivotal placebo-controlled trials and their open-label extension studies. The results show that 93% and 84% of patients were still alive after 1 and 2 years, respectively, after the start of treatment with TRACLEER. These estimates may be influenced by the initiation of epoprostenol treatment in 43/235 patients. In a subset of primary pulmonary hypertension (PPH) patients (n=169) the Kaplan-Meier survival estimates were 96% at 1 year and 89% at 2

years as compared to the predicted survival (calculated by the NIH registry formula) of 69% and 57% respectively.

Study AC-052-405: Patients with Pulmonary Arterial Hypertension associated with Congenital Heart Disease

A randomized, double-blind, multi-center, placebo-controlled study was conducted in 54 patients with WHO functional class III pulmonary arterial hypertension associated with Eisenmenger physiology associated with congenital heart disease (resulting in right to left shunt). Patients received TRACLEER 62.5 mg (n=37) or matching placebo (n=17) twice daily for 4 weeks and then TRACLEER 125 mg b.i.d. or matching placebo twice daily for 12 additional weeks.

In this study there were two primary endpoints. The first primary endpoint was to show that TRACLEER did not worsen the shunt or increase hypoxemia. The second primary endpoint was the mean change from baseline versus placebo in pulmonary vascular resistance indexed (PVRi) at Week 16. In addition, 6-minute walk distance was assessed.

After 16 weeks, TRACLEER increased mean oxygen saturation by 1.0% (95% CL= -0.7; 2.8) as compared to placebo, demonstrating that bosentan did not relevantly worsen hypoxemia. In comparison with placebo, treatment with TRACLEER statistically significantly decreased the indexed pulmonary vascular resistance by -472.0 ± 221.9 dyn·sec·cm^{-5} compared with placebo (95% CL= -917.6, -26.5; t-test, p=0.0383).

Treatment with TRACLEER was associated with a statistically significant improvement in walk distance with a placebo-corrected increases of 53.1 ± 19.2 m (95% CL=14.5, 91.7; t-test, p=0.0079) compared to placebo.

Study AC-052-362: Patients with Pulmonary Arterial Hypertension associated with Human Immunodeficiency Virus

In an open-label study without a control group, 16 epoprostenol-naïve patients with pulmonary arterial hypertension associated with human immunodeficiency virus (HIV) infection (stable, with CD4 cell >100 cells/mm^3) with WHO functional class III and IV were treated with TRACLEER 62.5 mg b.i.d. for 4 weeks and then up-titrated to 125 mg b.i.d. for the remaining 12 weeks of the study.

The distance in 6-minute walk test after 16 weeks of treatment with TRACLEER improved significantly by 91.4 ± 59.5 m from baseline (95% CL=59.7, 123.3; t-test, p<0.001). Improvement in Borg dyspnea index was also observed and was significantly reduced at week 16 (1.5 ± 1.6) compared with baseline (3.4 ± 2.5) (95% CL= -3.3, -0.5; t-test, p<0.013).

At baseline, 15 of the 16 patients were functional class III and one patient was class IV. After 4 weeks of treatment with TRACLEER at the 62.5 mg b.i.d. dose, 9 (56.3%) patients showed improvement in functional class. After an additional 12 weeks of treatment at the 125 mg b.i.d. dose, 14 of 16 patients (87.5%) improved from their baseline class including the one patient in class IV. Three patients improved from class III at baseline to class I and no patients deteriorated in functional class. One patient experienced clinical worsening in pulmonary arterial hypertension and was hospitalized.

Improvement from baseline to week 16 was observed with TRACLEER with a mean increase in cardiac index (0.88 L/min/m^2 ± 0.72; 95% CL=0.49, 1.26; t-test, p<0.001) and mean decreases in mean PAP (-11.0 mmHg; 95% CL= -17.4, -4.7; t-test, p=0.0002), and PVR (-339 dyn·sec/cm^{-5}; 95% CL= -454, -223; t-test, p< 0.001). This was an open-label study without a control group. These data should be interpreted cautiously.

Study AC-052-355: Patients Treated with Epoprostenol

The combination of TRACLEER and epoprostenol has been investigated in two studies: AC-052-355 (BREATHE-2) and AC-052-356 (BREATHE-3). AC-052-355 was a multicentre, randomized, double-blind, parallel-group trial of TRACLEER versus placebo in 33 patients with severe pulmonary arterial hypertension who were receiving concomitant epoprostenol therapy. AC-052-356 was an open-label, non-control trial in pediatric patients. Ten of the 19 pediatric patients were on concomitant TRACLEER and epoprostenol therapy during the 12-week trial.

Combination therapy with TRACLEER and epoprostenol was safe and well tolerated in children and adults. In children, TRACLEER treatment, with or without epoprostenol, resulted in significantly improved hemodynamics. In adults, combination therapy was associated with a larger improvement in hemodynamics compared to epoprostenol alone, although in no case did the differences between the groups reach statistical significance.

15 Microbiology

No microbiological information is required for this drug product.

16 Non-Clinical Toxicology

General toxicology

Animal toxicity studies
Bosentan had a low order of acute toxicity. The highest non-lethal doses were in the 125 to 250 mg/kg range by the i.v. and intraperitoneal routes of administration, 1,000 mg/kg or more by the subcutaneous route and 2,000 to >4,000 mg/kg by the oral route.

Repeated-dose toxicity - oral administration

Oral repeated-dose toxicity studies were conducted with bosentan in rats, dogs, and marmosets. Three repeated-dose toxicity studies of up to 6 months duration in rats and four studies of up to 12 months duration in dogs were conducted.

There was no substantial toxicity observed in any of the rat studies. Mild decreases (within normal limits) in red blood cell (RBC) parameters were noted that may be due to the vasodilating effects of bosentan and to the associated increase in plasma volume. Increases in liver weight were observed in rat studies; however, there was no histopathological evidence of hepatotoxicity in any of the repeated-dose studies in rats.

In most of the dog studies, a mild decrease in RBC parameters was also observed. In a 4-week study conducted at very high doses (500 and 1,000 mg/kg), increased serum liver enzymes and, histologically, bile duct proliferation and single cell necrosis were observed. In the 6-month study (10, 60 and 400 mg/kg), no significant toxicity was observed at doses up to 400 mg/kg. In the 12-month study (60, 180, and 500 mg/kg), histological changes indicative of a mild cholestasis and increased serum bile salts were observed at high doses. Mild increases in alkaline phosphatase, along with increased liver weights and hepatocellular hypertrophy, are compatible with the microsomal enzyme inducing properties of the drug in dogs. There were no

signs of centrolobular necrosis in any studies.

Oral administration (10, 80, and 500 mg/kg/day) to marmosets was generally well tolerated. No signs of systematic toxicity were observed.

Genotoxicity

The mutagenic and clastogenic potential of bosentan was evaluated in a comprehensive battery of tests *in vitro* and *in vivo*. In these tests, there was no evidence for any mutagenic or clastogenic activity with bosentan, including the lots with a higher level of impurities.

Carcinogenicity

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/m^2 basis). In the same study, doses greater than 2,000 mg/kg/day (about 32 times the [MRDH]) were associated with an increased incidence of colon adenomas in both males and females.

In rats, oral administration of bosentan for 2 years produced a small, significant increase in the combined incidence of thyroid follicular cell adenomas and carcinomas in male rats treated at doses of 3,000 mg/kg/day, about 600 times the human oral therapeutic dose in a 50-kg patient. There was no significant increase in the incidence of tumors in female rats or at sites other than the thyroid gland in male rats. There was evidence for a mild thyroid hormonal imbalance induced by bosentan in rats. There was no increase in mortality at any dose in mice and rats.

Bosentan is a microsomal enzyme inducer in mice; therefore the formation of liver tumors is not unexpected. Likewise, rats, particularly males, are susceptible to the development of thyroid follicular tumors secondary to thyroid hormone imbalance. No other rat or mouse tumor was considered related to bosentan treatment. The thyroid in rats and the liver in mice are among the most common tumor sites in carcinogenicity studies with pharmaceutical agents and this combination of tumors is found with many other drugs. Since an extensive battery of tests showed bosentan has no genotoxic potential, these findings are considered not to represent a relevant cancer risk.

Reproductive and developmental toxicology

In the fertility studies in rats, no effects were observed on mating performance or fertility, on the development of the preimplantation embryo, or on implantation. There were no changes in sperm count, motility, or viability or on testis weights.

Bosentan has been shown to be teratogenic in rats when given at doses about 6 times the human oral therapeutic dose in a 50-kg patient. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head and face and of the major vessels. No birth defects were observed in rabbits at doses of up to 1,500 mg/kg/day. Similarities in the pattern of malformations observed with other endothelin receptor antagonists and in endothelin knock-out mice indicate a class effect.

In a juvenile rat toxicity study, where rats were treated from Day 4 *post partum* up to adulthood, decreased absolute weights of testes and epididymides, and reduced number of sperm in epididymides were observed after weaning. The NOAEL was 21 times (at Day 21 *post partum*) and 2.3 times (Day 69 *post partum*) the human therapeutic exposure, respectively.

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

<u>Testicular findings in bosentan-treated rats</u>

In the 2-year carcinogenicity study in rats, an increase in the incidence of testicular tubular atrophy was observed in the treated groups as compared to the control groups. There was no increase in the incidence of testicular tubular atrophy in rats treated for 6 months or in dogs treated up to 12 months. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4,500 mg/kg/day. In various fertility studies, fertility was normal and sperm parameters (motility and counts), testis and epididymal weights, and histopathology were normal.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTRACLEER®

Bosentan tablets

This Patient Medication Information is written for the person who will be taking **TRACLEER**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **TRACLEER**, talk to a healthcare professional.

What TRACLEER is used for:

TRACLEER is used in adults to treat certain types of pulmonary arterial hypertension (PAH), which is high blood pressure in the blood vessels leading to your lungs.

How TRACLEER works:

TRACLEER is an endothelin receptor antagonist (ERA). It lowers high blood pressure in the lungs by relaxing the pulmonary arteries. This makes it easier for your heart to pump blood to the lungs and can help lower the chance of your disease getting worse.

The ingredients in TRACLEER are:

Medicinal ingredient(s): Bosentan monohydrate.

Non-medicinal ingredients: Corn starch, glyceryl behenate, magnesium stearate, povidone, pregelatinized starch, and sodium starch glycolate. The film-coating is composed of ethylcellulose, hydroxypropylmethylcellulose, iron oxide red, iron oxide yellow, talc, titanium dioxide and triacetin.

TRACLEER comes in the following dosage form(s):

Film-coated tablets: 62.5 mg and 125 mg bosentan (as bosentan monohydrate)

Do not use TRACLEER if:

- you are allergic to bosentan or to any of the other ingredients in TRACLEER.
- you were told by your healthcare professional that you have moderate to severe liver disease or abnormal liver test results.
- you are pregnant, think you are pregnant, plan to become pregnant, or could become pregnant because you are not using a reliable birth control method. TRACLEER can cause serious birth defects if taken during pregnancy.
- you are taking cyclosporine A (used to treat certain autoimmune diseases and to prevent rejection of organ transplants).
- you are taking glyburide (used to treat diabetes).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TRACLEER. Talk about any health conditions or problems you may have, including if you:

- have pulmonary veno-occlusive disease (PVOD), a condition where the blood vessels that carry blood from the lungs to the heart are blocked and are taking medicines that open your blood vessels (also known as vasodilators).
- have heart failure.
- have signs of fluid retention (buildup of fluids in the body). Your healthcare professional may prescribe you other medications to treat this condition before you start taking TRACLEER.
- have low blood pressure (less than 85 mm Hg).
- have liver problems.
- are breastfeeding or plan to breastfeed.

Other warnings you should know about:

Pregnancy and birth control:

- Do **not** take TRACLEER if you are pregnant. Taking TRACLEER during pregnancy may harm your unborn baby. Talk to your healthcare professional **right away** if you discover that you are pregnant during your treatment.
- If you are able to get pregnant:
    - you must have a negative pregnancy test before starting TRACLEER. Monthly pregnancy tests during treatment with TRACLEER are also recommended to allow the early detection of pregnancy.
    - your healthcare professional will advise you about the best birth control methods to use during your treatment. TRACLEER may make hormonal birth control methods (e.g., pills, injections, implant, vaginal rings, skin patches) ineffective. These methods on their own are not reliable. Therefore, if you use hormonal birth control methods you must also use a barrier method (e.g., female or male condoms, diaphragm, contraceptive sponge).
    - do **not** have unprotected sex. Tell your healthcare professional **right away** if you have unprotected sex, or if you think your birth control has failed.
    -

Breastfeeding: TRACLEER can pass into breast milk and may harm a breastfed baby. Therefore, TRACLEER is not recommended during breastfeeding. Talk to your healthcare professional about the best way to feed your baby during this time.

Fertility in men: It is possible that TRACLEER may lower your sperm count and affect your ability to have children. Speak with your healthcare professional if you plan on fathering a child, or have any questions or concerns about this.

Driving and using machines: TRACLEER can cause side effects such as low blood pressure, dizziness and blurry vision. Avoid driving, using machinery, or doing dangerous activities until you know how TRACLEER affects you.

Check-ups and testing: Some patients taking TRACLEER were found to have abnormal liver test results (increase in liver enzymes) and some patients developed anemia (decrease in red blood cells). Because these findings may not cause symptoms you can feel or observe yourself, your healthcare professional will do regular blood tests to monitor the health of your liver and the amount of red blood cells.

The blood test to monitor the health of your liver will be done:

- before you start taking TRACLEER.
- every month during your treatment or more frequently, if needed.

If you develop abnormal liver test results, your healthcare professional may reduce your dose or stop your treatment with TRACLEER. When your blood test results return to normal, your healthcare professional may decide to restart treatment with TRACLEER.

The blood test to monitor the amount of red blood cells in your blood will be done:
- before you start taking TRACLEER.
- after 1 month and after 3 months of treatment
- every 3 months during treatment thereafter.

If you develop anemia, your healthcare professional may decide to perform further tests to investigate the cause.

The blood tests mentioned above are an important part of your treatment. We suggest you write in a diary the date of your most recent test and also that of your next test to help you remember.

In addition, your healthcare professional should monitor you for signs of fluid retention (buildup of fluids in the body) during your treatment with TRACLEER. Tell your healthcare professional right away if you experience symptoms such as swelling of the legs or weight gain. If you have signs of fluid retention, your healthcare professional may investigate further to determine the cause. Fluid retention may be a sign of underlying heart failure and your healthcare professional may stop your treatment with TRACLEER.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Serious drug interactions:

Do not use TRACLEER if you take:

- cyclosporine A (used to treat certain autoimmune diseases and to prevent rejection of organ transplants)
- glyburide (used to treat diabetes)

The following may also interact with TRACLEER:

- medicines used to prevent the rejection of organ transplants such as tacrolimus or sirolimus.
- medicines used to treat fungal infections such as fluconazole, voriconazole, ketoconazole, or itraconazole.
- medicines used to treat HIV/AIDS such as ritonavir, lopinavir, or nevirapine.
- medicines known as “statins”, used to treat high blood cholesterol such as simvastatin, atorvastatin, lovastatin, rosuvastatin, or fluvastatin.
- medicines used to treat seizures such as carbamazepine, phenobarbital, or phenytoin.
- medicines used to treat erection problems such as sildenafil, or tadalafil.
- medicines taken by mouth to treat diabetes, such as glyburide.

- warfarin, used to treat and prevent blood clots.
- rifampicin, or rifampin, used to treat bacterial infections, including tuberculosis.
- hormonal birth control methods (e.g., pills, implant, injections, vaginal rings, skin patches).
- St. John's wort, a herbal remedy.

How to take TRACLEER:

- Always take TRACLEER exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Take TRACLEER twice daily (morning and evening) consistently, with or without food.
- Swallow the tablet with water.
- Suddenly stopping your treatment with TRACLEER may worsen your condition. Do not stop taking TRACLEER unless your healthcare professional tells you to. Your healthcare professional may tell you to reduce your dose over a few days before stopping completely.

Usual dose:

- **Weeks 1 to 4:** 62.5 mg twice daily.
- **Weeks 5 and after:** Your healthcare professional may increase your dose to 125 mg twice daily, depending on how you respond to TRACLEER.

Overdose:

If you think you, or a person you are caring for, have taken too much TRACLEER, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:
If you forget to take TRACLEER, take the missed dose as soon as you remember, then continue with the next dose at your usual time. Do not take a double dose to make up for the one that you missed.

Possible side effects from using TRACLEER:

These are not all the possible side effects you may have when taking TRACLEER. If you experience any side effects not listed here, tell your healthcare professional.

Side effects (regardless of reporting frequency) with TRACLEER may include:
- cold or flu like symptoms (runny nose, sore throat, sneezing, coughing, fever)
- inflammation of the sinuses
- nasal congestion
- ear infection
- feeling dizzy or like you are spinning
- blurry vision
- headache
- fever
- chest pain

- nausea or vomiting, heartburn, abdominal pain, diarrhea, constipation, rectal bleeding
- mouth ulcers, dry mouth
- loss of appetite
- skin rash, redness or discolouration, itchy skin, hives, dry skin, eczema
- bruising
- feeling weak, lack of energy
- joint pain
- flushing

Serious side effects and what to do about them

Frequency/Side-Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Common			
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Hypotension (low blood pressure): feeling dizzy or lightheaded, fainting, blurred vision, nausea, vomiting, fatigue		✓	
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff		✓	
Uncommon			
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, fever, nausea or vomiting, unusual dark urine, unusual tiredness, loss of appetite,		✓	
Unknown			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			✓
Pulmonary edema (excess fluid in the lungs): difficulty breathing that worsens with activity or when lying down, extreme shortness of breath, wheezing or gasping for breath, cold clammy skin, irregular heartbeat, cough that			✓

produces frothy sputum, blue-tinged lips			
Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature between 15ºC and 25ºC.
- Do not use after the expiry date stated on the blister.
- Keep out of reach and sight of children.

If you want more information about TRACLEER:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (innovativemedicine.jnj.com/canada); or by calling 1-800-567-3331 or 1-800-387-8781

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