TRACLEER™ (bosentan) contains 62.5 mg and 125 mg film-coated tablets.

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

WARNING: Potential liver injury TRACLEER™ causes at least 5-fold (upper limit of normal) to 10-fold (ULN) elevations of liver aminotransferases (ALT and AST) in about 11% of patients, sometimes leading to fatalities in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly (see WARNINGS: Potential Liver Injury and DOSAGE AND ADMINISTRATION). To date, in a wide range of clinical trials, elevations have been reversible, within a few days to 3 weeks, either spontaneously or after dose reduction or discontinuation, and without sequelae.

Elevations in aminotransferases require dose reduction (see DOSAGE AND ADMINISTRATION). TRACLEER™ should be generally avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult.

If liver aminotransferase elevations are accompanied by other symptoms of liver injury (e.g., nausea, vomiting, liver pain, jaundice, or unusual fatigue or lethargy) or if there is an abnormal physical examination of the liver, the TRACLEER™ tablet should be withdrawn. There is no experience with the re-introduction of TRACLEER™ in these circumstances.

CONTRAINDICATIONS: Pregnancy TRACLEER™ (bosentan) is very likely to produce fetal defects if used by pregnant women; as such, this effect has been seen consistently in animal studies (see CONTRAINDICATIONS). Therefore, pregnancy must be excluded before the start of treatment with TRACLEER™ and prevented thereafter by the use of a reliable method of contraception. Hormonal contraceptives, including oral, injectable and implantable contraceptives should not be used as means of contraception prior to these methods may not be effective in patients receiving TRACLEER™ (see PRECAUTIONS: Drug Interactions). Monthly pregnancy tests should be performed.

Because of potential liver injury and in an effort to make the chance of fetal exposure to TRACLEER™ minimal, TRACLEER™ may be prescribed only through the TRACLEER™ Access Program by calling 1 866 89 352 35 44.

DESCRIPTION Bosentan is the first of a new drug class, an endothelin receptor antagonist.

TRACLEER™(bosentan) belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. It is designated chemically as 4-tet-butyl-N-[2-(hydroxyethyl)-5-(2-methoxyphenyl)-3,2'-bipyrimidinyl]-4-benzylamino monohydrate and has the following structural formula:

![Structural formula of bosentan](image)

Bosentan has a molecular weight of 568.64 and a molecular formula of C₂₆H₂₃NO₁₂S₅. TRACLEER™ is a white to yellowish powder. It is poorly soluble in water (1.0 mg/100 ml) and in aqueous solutions at low pH (0.08 mg/ml at pH 1.2 and 0.2 mg/ml at pH 5.0). Solubility increases at higher pH values (43 mg/ml at pH 7.5). In the solid state, bosentan is very stable, is not hygroscopic and is not readily sensitive.

TRACLEER™ is available as 62.5 mg and 125 mg film-coated tablets for oral administration, and contains the following excipients: corn starch, pregelatinized starch, sodium starch glycolate, pregelatinized starch, magnesium stearate, hydroxypropylmethylcellulose, talc, titanium dioxide, iron oxide red, and hydroxypropyl cellulose. Each TRACLEER™ 62.5 mg tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan. Each TRACLEER™ 125 mg tablet contains 125.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan.

CLINICAL PHARMACOLOGY Mechanism of Action

Endothelin-1 (ET-1) is a neurotransmitter, the effects of which are mediated by binding to ET₁ and ET₂ receptors; bosentan is a competitive antagonist at both receptor types (ET₁ and ET₂). Bosentan has a slightly higher affinity for ET₁ receptors than for ET₂ receptors.

Pharmacokinetics General

After oral administration, maximum plasma concentrations of bosentan are attained within 3-6 hours and the terminal elimination half-life (t ½) is about 5 days. The bioavailability of bosentan in patients with portal arterial hypertension, but exposure is expected to be greater for plasma bosentan concentrations in patients with severe chronic heart failure. Absorption and Distribution The absolute bioavailability of bosentan in normal volunteers is approximately 90%. The volume of distribution is about 18 L. Bosentan is highly bound (>98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

Metabolism and Elimination Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%-20% of the total bosentan. Bosentan is an inducer of CYP3A4 (CYP3A4 and possibly also of CYP2C19). Total clearance after a single intravenous dose is about 8 L/hr. Upon multiple dosing, plasma concentrations decrease gradually to 50%-65% of those seen with single-dose administration, probably the effect of auto-induction of the metabolizing liver enzymes. Steady-state is reached within 5-3 days. Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine.

Special Populations It is not known whether bosentan pharmacokinetics is influenced by sex, weight, race, or age. Liver Function Impairment The influence of liver impairment on the pharmacokinetics of bosentan has not been evaluated. In rat liver, in vivo and in vitro evidence showing extensive hepatic metabolism of bosentan suggests that liver impairment would significantly increase exposure of bosentan. CLCR (clearance of creatinine) was assessed in patients during the use of TRACLEER™ in patients with mildly impaired liver function. TRACLEER™ should generally be avoided in patients with severe liver abnormalities and/or elevated aminotransferases (>3 x ULN). See WARNINGS: Drug Interactions. Renal Impairment In patients with severe renal impairment (creatinine clearance < 15 ml/min), plasma concentrations of bosentan were unchanged and plasma concentrations of the three metabolites were increased compared to people with normal renal function. These differences do not appear to be clinically important (see DOSAGE AND ADMINISTRATION). Clinical Studies Two randomized, double-blind, multi-center, placebo-controlled trials were conducted in 32 and 213 patients. The larger study (BREATHE-1) compared 2 doses (125 mg b.i.d. and 250 mg b.i.d.) of TRACLEER™ with placebo. The smaller study (Study 351) compared 125 mg b.i.d. with placebo. Patients had severe WHO functional class III-IV (LVF class IV) pulmonary arterial hypertension: primary pulmonary hypertension (32%), pulmonary hypertension secondary to scleroderma or other connective tissue diseases (21%), or other causes (47%). There were no patients with pulmonary hypertension secondary to other conditions such as HIV disease, or severe pulmonary embolism.

In both studies, TRACLEER™ or placebo was added to patient's current therapy, which could have included a combination of digoxin, anticoagulants, diuretics, and vasodilators, and/or oral or parenteral blood pressure blocking agents (ACE inhibitors), but not diuretics. TRACLEER™ was given at a dose of 62.5 mg b.i.d. for 4 weeks and then at 125 mg b.i.d. or 250 mg b.i.d. for either 12 (BREATHE-1) or 6 (Study 351) additional weeks. The primary study endpoint was 6-minute walk distance. In addition, symptoms and functional status (WHO) were assessed. Hemodynamic measurements were made at 12 weeks in Study 351. The mean age was about 49 years. About 80% of patients were white, about 60% were women, and 40% were Caucasian. Patients had been diagnosed with pulmonary hypertension for a mean of 2.4 years.

Submaximal Exercise Capacity Results of the 6-minute walk distance at 3 months (Study 351) or 4 months (BREATHE-1) are shown in Table 1.

In both trials, treatment with TRACLEER™ resulted in a significant increase in exercise capacity. The improvement in walk distance was apparent after 1 month of therapy (62.5 mg b.i.d.) and fully developed by about 2 months of treatment (Figure 1). It was maintained at 6 months of therapy and 7 months of double-blind withdrawal. Walking distance was somewhat greater with 250 mg b.i.d. than with 62.5 mg b.i.d., but the potential for increased liver injury caused this dose not to be recommended (see DOSAGE AND ADMINISTRATION).

Symptoms and Functional Status Symptom improvements for PAH, discontinuation of therapy because of PAH-related symptoms, and/or severe PAH disease etiology, but the studies had little power to detect such differences.

Hemodynamic Changes In both studies, all prespecified hemodynamic parameters were assessed in Study 351. Treatment with TRACLEER™ led to a significant reduction in pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR), and right atrial pressure (RAP) (Table 2).

Table 1. Effects of bosentan on 6-minute walk distance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline</th>
<th>Week 8</th>
<th>Week 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRACLEER™</td>
<td>265.7±57.3</td>
<td>228.0±35.3</td>
<td>206.3±35.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>266.7±57.3</td>
<td>254.7±57.3</td>
<td>246.7±57.3</td>
</tr>
</tbody>
</table>

Figure 1. Mean Change in 6-min Walk Distance (BREATHE-1)
Liver transaminase levels must be measured prior to initiation of treatment and then monthly. If elevation in liver function tests occurs, changes in monitoring and treatment must be initiated (see DOSAGE AND ADMINISTRATION). In clinical trials of bosentan, elevations in alanine aminotransferase are accompanied by clinical symptoms of liver injury (nausea, vomiting, fever, abdominal pain, jaundice) and such elevations have no effect on plasma levels of bosentan.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Tests of dietary administration of bosentan to mice produced an increased incidence of hepatic/202

lar adenomas and carcinomas in male as doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg b.i.d., on a mg/m² basis). In the same study, greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with a statistically significant increase in male brain astrocytomas in males at doses as low as 500 mg/kg/day (about 10 times the MRHD, a statistically significant increase in male brain astrocytomas, and an increase in female astrocytomas). There was no evidence for any mutagenic or clastogenic activity of bosentan.

Impairment of Fertility/Teutical Function

Many endocrine receptor antagonists have profound effects on the endocrine system in female and male testes in animals. These drugs have been shown to change all hormone values and to produce anomalies in fertility. In a study where male rats were treated with bosentan at oral doses of up to 100 mg/kg/day (about 1.6 times the MRHD), and the lowest dose of the drug remained within normal limits in 68% of bosentan-treated patients compared to 76% of placebo treated patients. Input from a gynecologist or similar expert is recommended in cases of breast enlargement or breast tenderness. It is recommended that hemoglobin concentrations are monitored in patients taking TRACLEER™. Baseline hemoglobin concentrations remained within normal limits in 68% of patients taking TRACLEER™. Baseline hemoglobin concentrations were increased by about 30-fold. Steady-state concentrations of bosentan increased 30-fold, resulting in a 62.5 mg b.i.d. for 4 weeks and then increased to 3 to 7 days) should be interrupted. If TRACLEER™ is re-introduced it should be at the starting dose. Elevations in transaminase levels should be checked within 3 days and thereafter according to the recommendations above. Liver transaminase elevations are accompanied by clinical symptoms of liver injury (nausea, vomiting, fever, abdominal pain, jaundice) and such elevations have no effect on plasma levels of bosentan.

Use in Women of Child-bearing Potential

TRACLEER™ treatment should only be initiated in women of child-bearing potential when there is no pregnancy test and only in those who practice adequate contraception that does not rely solely upon hormonal contraceptives, including oral, injectable or implantable contraceptives (see DRUG INTERACTIONS: Hormonal contraceptives, Including Oral, Injectable and Implantable Contraceptives). Input from a gynecologist or similar expert on adequate contraception should be sought as needed. Urine or serum pregnancy tests should be obtained monthly in women of child-bearing potential taking TRACLEER™.

Dosage Adjustment in Renal Impaired Patients

The effect of renal impairment on the pharmacoki- netics of bosentan is small and does not require adjusting.