

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Tracleer 62.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 62.5 mg bosentan (as monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablets):

Orange-white, round, biconvex, film-coated tablets, embossed with “62,5” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:

- Primary (idiopathic and familial) PAH
- PAH secondary to scleroderma without significant interstitial pulmonary disease
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger’s physiology

Some improvements have also been shown in patients with PAH WHO functional class II (see section 5.1).

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see section 5.1).

4.2 Posology and method of administration

Tablets are to be taken orally morning and evening, with or without food. The film-coated tablets are to be swallowed with water.

Pulmonary arterial hypertension

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

In adult patients, Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

For paediatric patients aged 2 years or older, the optimal maintenance dose has not been defined in well-controlled studies. However, pediatric pharmacokinetic data have shown that bosentan plasma concentrations in children were on average lower than in adult patients and were not increased by increasing the dose of Tracleer above 2 mg/kg twice daily (see section 5.2). Based on these pharmacokinetic results, higher doses are unlikely to be more effective, and greater adverse event rates cannot formally be excluded in young children if the dose is increased. No clinical study has been conducted to compare the efficacy/safety ratio of 2 mg/kg to 4 mg/kg twice daily in children.

There is only limited clinical experience in paediatric patients under 2 years of age.

In the case of clinical deterioration (e.g., decrease in 6-minute walk test distance by at least 10% compared with pre-treatment measurement) despite Tracleer treatment for at least 8 weeks (target dose for at least 4 weeks), alternative therapies should be considered. However, some patients who show no response after 8 weeks of treatment with Tracleer may respond favourably after an additional 4 to 8 weeks of treatment.

In the case of late clinical deterioration despite treatment with Tracleer (i.e., after several months of treatment), the treatment should be re-assessed. Some patients not responding well to 125 mg twice daily of Tracleer may slightly improve their exercise capacity when the dose is increased to 250 mg twice daily. A careful risk/benefit assessment should be made, taking into consideration that the liver toxicity is dose dependent (see sections 4.4 and 5.1).

Discontinuation of treatment

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. However, to avoid the possible occurrence of harmful clinical deterioration due to potential rebound effect, gradual dose reduction (halving the dose for 3 to 7 days) should be considered. Intensified monitoring is recommended during the discontinuation period. If the decision to withdraw Tracleer is taken, it should be done gradually while an alternative therapy is introduced.

Systemic sclerosis with ongoing digital ulcer disease

Treatment should only be initiated and monitored by a physician experienced in the treatment of systemic sclerosis.

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

Controlled clinical study experience in this indication is limited to 6 months (see section 5.1).

The patient's response to treatment and need for continued therapy should be re-evaluated on a regular basis. A careful risk/benefit assessment should be made, taking into consideration the liver toxicity of bosentan (see sections 4.4 and 4.8).

There are no data on the safety and efficacy in patients under the age of 18 years. Kinetic data are not available for Tracleer in young children with this disease.

Special populations

Dosage in hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment (i.e., Child-Pugh class A) (see section 5.2). Tracleer is contraindicated in patients with moderate to severe liver dysfunction (see sections 4.3, 4.4 and 5.2).

Dosage in renal impairment

No dose adjustment is required in patients with renal impairment. No dose adjustment is required in patients undergoing dialysis (see section 5.2).

Dosage in elderly patients

No dose adjustment is required in patients over the age of 65 years.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients

- Moderate to severe hepatic impairment i.e. Child-Pugh-class B or C (see section 5.2)
- Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal (see section 4.4)
- Concomitant use of cyclosporine A (see section 4.5)
- Pregnancy (see section 4.4 and 4.6)
- Women of childbearing potential who are not using reliable methods of contraception (see sections 4.4, 4.5 and 4.6)

4.4 Special warnings and precautions for use

The efficacy of Tracleer has not been established in patients with severe pulmonary arterial hypertension. Transfer to a therapy that is recommended at the severe stage of the disease (e.g., epoprostenol) should be considered if the clinical condition deteriorates (see section 4.2).

The benefit/risk balance of bosentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension.

Tracleer should only be initiated if the systemic systolic blood pressure is higher than 85 mmHg.

Tracleer has not been shown to have a beneficial effect on the healing of existing digital ulcers.

Liver function

Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment but may also occur late in treatment (see section 4.8). These increases may be partly due to competitive inhibition of the elimination of bile salts from hepatocytes but other mechanisms, which have not been clearly established, are probably also involved in the occurrence of liver dysfunction. The accumulation of bosentan in hepatocytes leading to cytolysis with potentially severe damage of the liver, or an immunological mechanism, are not excluded. Liver dysfunction risk may also be increased when medicinal products that are inhibitors of the bile salt export pump (BSEP), e.g., rifampicin, glibenclamide and cyclosporine A (see sections 4.3 and 4.5), are co-administered with bosentan, but limited data are available.

Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Tracleer. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase.

Recommendations in case of ALT/AST elevations

ALT/AST levels	Treatment and monitoring recommendations
> 3 and $\leq 5 \times$ ULN	Confirm by another liver test; if confirmed, reduce the daily dose or stop treatment (see section 4.2), monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider continuing or re-introducing Tracleer according to the conditions described below.
> 5 and $\leq 8 \times$ ULN	Confirm by another liver test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider re-introducing Tracleer according to the conditions described below.
> 8 \times ULN	Treatment must be stopped and re-introduction of Tracleer is not to be considered.

In case of associated clinical symptoms of liver injury, i.e., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), treatment must be stopped and re-introduction of Tracleer is not to be considered.

Re-introduction of treatment

Re-introduction of treatment with Tracleer should only be considered if the potential benefits of treatment with Tracleer outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the guidelines detailed in section 4.2. **Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.**

ULN= Upper Limit of Normal

Haemoglobin concentration

Treatment with bosentan has been associated with dose-related decreases in haemoglobin concentration (see section 4.8). In placebo-controlled studies, bosentan-related decreases in haemoglobin concentration were not progressive, and stabilised after the first 4–12 weeks of treatment. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first 4 months, and quarterly thereafter. If a clinically relevant decrease in haemoglobin concentration occurs, further evaluation and investigation should be undertaken to determine the cause and need for specific treatment. In the post-marketing period, cases of anaemia requiring red blood cell transfusion have been reported (see section 4.8).

Women of child-bearing potential

Tracleer treatment must not be initiated in women of child-bearing potential unless they practice reliable contraception (see section 4.5) and the result of the pre-treatment pregnancy test is negative (see section 4.6).

Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods 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 section 4.5). Therefore, women of child-bearing 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 gynaecologist 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.

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema 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 oedema in patients treated with Tracleer who had a suspected diagnosis of pulmonary veno-occlusive disease.

Pulmonary arterial hypertension patients with concomitant left ventricular failure

No specific study has been performed in patients with pulmonary hypertension and concomitant left ventricular dysfunction. However, 1,611 patients (804 Tracleer- and 807 placebo-treated patients) with

severe chronic heart failure (CHF) were treated for a mean duration of 1.5 years in a placebo-controlled study (study AC-052-301/302 [ENABLE 1 & 2]). In this study there was an increased incidence of hospitalisation due to CHF during the first 4 - 8 weeks of treatment with Tracleer, which could have been the result of fluid retention. In this study, fluid retention was manifested by early weight gain, decreased haemoglobin concentration and increased incidence of leg oedema. At the end of this study, there was no difference in overall hospitalisations for heart failure nor in mortality between Tracleer- and placebo-treated patients. Consequently, it is recommended that patients be monitored for signs of fluid retention (e.g., weight gain), especially if they concomitantly suffer from severe systolic dysfunction. Should this occur, starting treatment with diuretics is recommended, or the dose of existing diuretics should be increased. Treatment with diuretics should be considered in patients with evidence of fluid retention before the start of treatment with Tracleer.

Pulmonary arterial hypertension associated with HIV infection

There is limited clinical study experience with the use of Tracleer in patients with PAH associated with HIV infection, treated with antiretroviral medicinal products (see section 5.1). An interaction study between bosentan and lopinavir+ritonavir in healthy subjects showed increased plasma concentrations of bosentan with the maximum level during the first 4 days of treatment (see section 4.5). When treatment with Tracleer is initiated in patients who require ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be closely monitored with special attention, at the beginning of the initiation phase, to the risk of hypotension and to liver function tests. An increased long-term risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. Due to the potential for interactions related to the inducing effect of bosentan on CYP450 (see section 4.5), which could affect the efficacy of antiretroviral therapy, these patients should also be monitored carefully regarding their HIV infection.

Concomitant use with other medicinal products

Glibenclamide: Tracleer should not be used concomitantly with glibenclamide, due to an increased risk of elevated liver aminotransferases (see section 4.5). An alternative antidiabetic medicinal product should be used in patients in whom an antidiabetic treatment is indicated.

Fluconazole: concomitant use of Tracleer with fluconazole is not recommended (see section 4.5). Although not studied, this combination may lead to large increases in plasma concentrations of bosentan.

Rifampicin: co-administration of Tracleer with rifampicin is not recommended (see section 4.5).

Concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor should be avoided (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Bosentan is an inducer of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4. *In vitro* data also suggest an induction of CYP2C19. Consequently, plasma concentrations of substances metabolised by these isoenzymes will be decreased when Tracleer is co-administered. The possibility of altered efficacy of medicinal products metabolised 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 is metabolised by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been studied. The combination should be used with caution. Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor

(such as ketoconazole, itraconazole and ritonavir) and a CYP2C9 inhibitor (such as voriconazole) with Tracleer is not recommended.

Specific interaction studies have demonstrated the following:

Cyclosporine A: co-administration of Tracleer and cyclosporine A (a calcineurin inhibitor) is contraindicated (see section 4.3). Indeed, when co-administered, initial trough concentrations of bosentan were approximately 30-fold higher than those measured after bosentan alone. At steady state, bosentan plasma concentrations were 3- to 4-fold higher than with bosentan alone. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. The blood concentrations of cyclosporine A (a CYP3A4 substrate) decreased by approximately 50%. This is most likely due to induction of CYP3A4 by bosentan.

Tacrolimus, sirolimus: co-administration of tacrolimus or sirolimus and Tracleer has not been studied in man but co-administration of tacrolimus or sirolimus and Tracleer may result in increased plasma concentrations of bosentan in analogy to co-administration with cyclosporine A. Concomitant Tracleer may reduce the plasma concentrations of tacrolimus and sirolimus. Therefore, concomitant use of Tracleer and tacrolimus or sirolimus is not advisable. Patients in need of the combination should be closely monitored for adverse events related to Tracleer and for tacrolimus and sirolimus blood concentrations.

Glibenclamide: co-administration of Tracleer 125 mg twice daily for 5 days decreased the plasma concentrations of glibenclamide (a CYP3A4 substrate) by 40%, with potential significant decrease of the hypoglycaemic effect. The plasma concentrations of bosentan were also decreased by 29%. In addition, an increased incidence of elevated aminotransferases was observed in patients receiving concomitant therapy. Both glibenclamide and bosentan inhibit the bile salt export pump, which could explain the elevated aminotransferases. In this context, this combination should not be used (see section 4.4). No drug-drug interaction data are available with the other sulfonylureas.

Hormonal contraceptives: Co-administration of Tracleer 125 mg twice daily for 7 days with a single dose of oral contraceptive containing norethisterone 1 mg + ethinyl estradiol 35 mcg decreased the AUC of norethisterone and ethinyl estradiol by 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, 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 sections 4.4, 4.6).

Warfarin: co-administration of bosentan 500 mg twice daily for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29% and 38%, respectively. Clinical experience of concomitant administration of bosentan with warfarin in patients with pulmonary arterial hypertension did not result in clinically relevant changes in International Normalized Ratio (INR) or warfarin dose (baseline versus end of the clinical studies). In addition, the frequency of changes in warfarin dose during the studies due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. No dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated but intensified monitoring of INR is recommended, especially during bosentan initiation and the up-titration period.

Simvastatin: co-administration of Tracleer 125 mg twice daily for 5 days decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β -hydroxy acid metabolite by 34% and 46%, respectively. The plasma concentrations of bosentan were not affected by concomitant simvastatin. Monitoring of cholesterol levels and subsequent dosage adjustment should be considered.

Ketoconazole: co-administration of Tracleer 62.5 mg twice daily for 6 days and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan approximately 2-fold. No dose adjustment of Tracleer is considered necessary. Although not demonstrated through *in vivo* studies, similar increases in bosentan plasma concentrations are expected with the other potent CYP3A4 inhibitors (such as itraconazole and ritonavir). However, when combined with a CYP3A4 inhibitor,

patients who are poor metabolisers of CYP2C9 are at risk of increases in bosentan plasma concentrations that may be of higher magnitude, thus leading to potential harmful adverse events.

Rifampicin: co-administration in 9 healthy subjects of Tracleer 125 mg twice daily for 7 days and rifampicin, a potent inducer of CYP2C9 and CYP3A4, decreased the plasma concentrations of bosentan by 58%, and this decrease could achieve almost 90% in an individual case. A subsequent significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. Data on other CYP3A4 inducers, e.g. carbamazepine, phenobarbital, phenytoin and St. John's wort are lacking, but their concomitant administration is expected to lead to reduced systemic exposure to bosentan. A clinically significant reduction of efficacy cannot be excluded.

Epoprostenol: limited data obtained from a study (AC-052-356, BREATHE-3) in which 10 paediatric patients received the combination of Tracleer and epoprostenol indicate 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 section 5.1).

Sildenafil: co-administration of Tracleer 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease of the sildenafil AUC and a 50% increase of the bosentan AUC. Caution is recommended in case of co-administration.

Digoxin: co-administration of bosentan 500 mg twice daily for 7 days decreased the AUC, C_{max} and C_{min} of digoxin by 12%, 9% and 23%, respectively. The mechanism for this interaction may be induction of P-glycoprotein. This interaction is unlikely to be of clinical relevance.

Antiretroviral agents :

Lopinavir+Ritonavir (and other boosted protease inhibitors): Co-administration of Tracleer 125 mg twice daily and lopinavir+ritonavir 400+100mg twice daily during 9.5 days in healthy volunteers, resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after Tracleer administered alone. On day 9, plasma concentrations of bosentan were approximately 5-fold higher 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. When administered concomitantly with lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be monitored.

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. Appropriate monitoring of the HIV therapy is recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors (see section 4.4.).

Other antiretroviral agents:

No specific recommendation can be made with regard to other available antiretroviral agents due to the lack of data. It is emphasized that due to a marked hepatotoxicity of nevirapine that could cumulate with bosentan liver toxicity, this combination is not recommended.

4.6 Pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (teratogenicity, embryotoxicity, see section 5.3). There are no reliable data on the use of Tracleer in pregnant women. The potential risk for humans is still unknown. Tracleer is contraindicated in pregnancy (see section 4.3).

Use in women of child-bearing potential

Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods 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 section 4.5). Therefore, women of childbearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but must 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 gynaecologist 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.

Use during lactation

It is not known whether bosentan is excreted into human breast milk. Breast-feeding is not recommended during treatment with Tracleer.

4.7 Effects on ability to drive and use machines

No studies on the effect of Tracleer on the ability to drive and use machines have been performed. Tracleer may cause dizziness, which could influence the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions

Integrated findings from placebo-controlled studies

In eight placebo-controlled studies, six of which were for indications other than pulmonary arterial hypertension, a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The foreseen duration of treatment ranged from 2 weeks to 6 months. The adverse drug reactions that occurred more frequently on bosentan than on placebo ($\geq 3\%$ of bosentan-treated patients, with $\geq 2\%$ difference) were headache (15.8% vs 12.8%), flushing (6.6% vs 1.7%), abnormal hepatic function (5.9% vs 2.1%), leg oedema (4.7% vs 1.4%), and anaemia (3.4% vs 1.0%), all of which were dose related.

Adverse reactions/undesirable effects are ranked according to frequency using the following convention : Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Frequency categories do not account for other factors, including varying study duration, pre-existing conditions, and baseline patient characteristics. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Placebo-controlled studies in primary (idiopathic/familial) PAH and PAH associated with connective tissue diseases

The table below shows the adverse drug reactions, defined as adverse events reported in $\geq 3\%$ of patients and more frequently on bosentan (125 and 250 mg twice daily) in three placebo-controlled trials (bosentan n = 258, placebo n = 172) in PAH.

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection, Nasopharyngitis, Respiratory tract infection,

		Sinusitis
Blood and lymphatic system disorders	Common	Anaemia,
Nervous system disorders	Very common Common	Headache ¹ Syncope
Cardiac disorders	Common	Palpitations
Vascular disorders	Common	Hypotension, Flushing
Hepatobiliary disorders	Very common	Liver function test abnormal
Musculoskeletal and connective tissue disorder	Common	Arthralgia
General disorders and administration site conditions	Very common Common	Oedema ² , Fluid retention Chest pain

¹ Headache was reported in 15.1% of patients on bosentan and 14.5% of patients on placebo.

² Oedema or fluid retention was reported in 11.6% of patients on bosentan and 9.9% of patients on placebo.

Treatment discontinuations due to adverse events, during the clinical studies in patients with pulmonary arterial hypertension, at doses of 125 and 250 mg twice daily, occurred with the same frequency (5.8%) in bosentan and placebo-treated patients.

Placebo-controlled study in PAH associated with congenital heart disease (BREATHE-5)

The safety profile of Tracleer in this population was similar to that observed in the pivotal studies in patients with PAH. Adverse events that occurred in a greater proportion of patients on Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily (n = 37) than on placebo (n = 17) included peripheral oedema (18.9% vs. 5.9%), headache (13.5% vs. 11.8%), palpitations (10.8% vs. 0%), dizziness (8.1% vs. 5.9%) and chest pain (8.1% vs. 0%). Four patients discontinued due to adverse events, two (5.4%) in the bosentan group and two (11.8%) in the placebo group.

Uncontrolled study in patients with PAH associated with HIV infection (BREATHE-4)

The safety profile in this population (n = 16) when treated with Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily was similar to that observed in the pivotal studies in patients with PAH. The most frequent adverse events were peripheral oedema (31%), headache (19%), abnormal liver function (13%), muscle cramps (13%), fluid retention (13%) and vomiting (13%). Haematological abnormalities (anaemia and decrease in neutrophil count) were observed in some patients (see section 4.4).

Uncontrolled trials in paediatric patients (BREATHE-3; FUTURE 1)

The safety profile in this population (BREATHE-3: n = 19, Tracleer 2 mg/kg twice daily; treatment duration 12 weeks; FUTURE 1: n = 36, Tracleer 2 mg/kg twice daily for 4 weeks followed by 4 mg/kg twice daily; treatment duration 12 weeks) was similar to that observed in the pivotal trials in adult patients with PAH. In BREATHE-3, the most frequent adverse events were flushing (21%), headache, and abnormal hepatic function (each 16%). In FUTURE-1, the most frequent adverse events were infections (33%) and abdominal pain/discomfort (19%). There were no cases of liver enzyme elevations in the FUTURE-1 study.

Placebo-controlled studies in digital ulcers

The table below shows the adverse drug reactions, defined as adverse events reported in $\geq 3\%$ of patients and more frequently on bosentan (125 mg twice daily) in the two pivotal placebo-controlled studies in digital ulcers (bosentan n = 175, placebo n = 133).

System organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Infected skin ulcer, Urinary tract infection

Blood and lymphatic system disorders	Common	Anaemia, Haemoglobin decrease
Vascular disorders	Common	Flushing
Gastrointestinal disorders	Common	Gastrooesophageal reflux disease, Diarrhoea, Abdominal pain, Constipation
Hepatobiliary disorders	Very common	Liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Erythema
Musculoskeletal and connective tissue disorder	Common	Pain in extremity, Back pain
General disorders and administration site conditions	Very common	Oedema, Fluid retention

Laboratory abnormalities

Liver test abnormalities

Bosentan has been associated with dose-related elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases. In the clinical programme, liver enzyme changes generally occurred within the first 26 weeks of treatment, usually developed gradually, and were mainly asymptomatic. They returned, in all cases during the clinical programme, to pre-treatment levels, without sequelae, within a few days to 9 weeks either spontaneously or after dose reduction or discontinuation. In the post-marketing period rare cases of liver cirrhosis and liver failure have been reported (see end of section 4.8).

The mechanism of this adverse effect is unclear. These elevations in aminotransferases may reverse spontaneously while continuing treatment with the maintenance dose of Tracleer or after dose reduction, but interruption or cessation may be necessary (see section 4.4).

In the eight integrated placebo-controlled studies, six of which were for indications other than pulmonary arterial hypertension, elevations in liver aminotransferases by greater than 3 times the upper limit of normal (ULN) were observed in 11.2% of the bosentan-treated patients as compared to 1.8% of the placebo-treated patients. Bilirubin increases to $> 3 \times$ ULN were associated with aminotransferase increases ($> 3 \times$ ULN) in 2 of 658 (0.3%) of patients treated with bosentan. Nine of the 74 bosentan-treated patients who had elevated liver aminotransferases ($> 3 \times$ ULN) also had symptoms such as abdominal pain, nausea/vomiting, and fever.

In studies in patients with pulmonary arterial hypertension, the incidence of elevated liver aminotransferases ($> 3 \times$ ULN) was 12.8% in bosentan-treated patients (N = 257), 12.3% in patients treated with 125 mg twice daily and 14.3% in patients treated with 250 mg twice daily. Eight-fold increases were seen in 3.7% of pulmonary arterial hypertension patients on 125 mg twice daily and 7.1% of pulmonary arterial hypertension patients on 250 mg twice daily.

In the two studies in patients with digital ulcers the incidence of elevated liver aminotransferases ($> 3 \times$ ULN) was 11.3% in bosentan-treated patients (N = 168) compared with 0.8% in placebo-treated patients (N = 129). Elevations to $> 8 \times$ ULN were seen in 2.4% of bosentan-treated patients with digital ulcers.

Haemoglobin

The mean decrease in haemoglobin concentration from baseline to study completion for the bosentan-treated patients was 0.9 g/dl and for the placebo-treated patients was 0.1 g/dl.

In eight placebo-controlled studies, clinically relevant decreases in haemoglobin (> 15% decrease from baseline resulting in values < 11 g/dl) were observed in 5.6% of bosentan-treated patients as compared with 2.6% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg twice daily, clinically relevant decreases in haemoglobin occurred in 3.0% and 1.3% of the bosentan- and placebo-treated patients, respectively.

In the two studies in patients with digital ulcers, clinically relevant decreases in haemoglobin (decrease from baseline resulting in haemoglobin values < 10 g/dL) were observed in 4.2% of bosentan-treated patients (N = 167), compared with 3.1% of placebo-treated patients (N = 129).

In the post-marketing period cases of anaemia requiring red blood cell transfusion have been reported (see end of section 4.8).

Post-marketing experience

The majority of adverse events reported during the post-marketing period have been similar to those reported in clinical studies.

Undesirable effects are ranked under headings of frequency using the following convention; very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$).

Gastrointestinal disorders:

Common: nausea

Uncommon: vomiting, abdominal pain, diarrhoea

Hepato-biliary disorders:

Uncommon: aminotransferase elevations associated with hepatitis and/or jaundice

Rare: liver cirrhosis, liver failure

Skin and subcutaneous tissue disorders:

Uncommon: hypersensitivity reactions including dermatitis, pruritus and rash

Immune system disorders:

Rare: anaphylaxis and/or angioedema

Blood and lymphatic system disorders:

Common: anaemia or haemoglobin decreases, sometimes requiring red blood cell transfusion (see section 4.4)

Uncommon: thrombocytopenia

Rare: neutropenia, leukopenia

In the post-marketing period rare cases of unexplained hepatic cirrhosis were reported after prolonged therapy with Tracleer in patients with multiple co-morbidities and therapies with medicinal products. There have also been rare reports of liver failure. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with Tracleer (see section 4.4).

4.9 Overdose

Bosentan has been administered as a single dose of up to 2400 mg to healthy subjects and up to 2000 mg/day for 2 months in patients with a disease other than pulmonary hypertension. The most common adverse event was headache of mild to moderate intensity.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antihypertensives, ATC code: C02KX01

Mechanism of action

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (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-1 (ET-1) is one of the most potent vasoconstrictors known and can also promote fibrosis, cell proliferation, cardiac hypertrophy, and remodeling and is pro-inflammatory. These effects are mediated by endothelin binding to ET_A and ET_B receptors located in the endothelium and vascular smooth muscle cells. ET-1 concentrations in tissues and plasma are increased in several cardiovascular disorders and connective tissue diseases, including pulmonary arterial hypertension, scleroderma, acute and chronic heart failure, myocardial ischaemia, systemic hypertension and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In pulmonary arterial hypertension and heart failure, in the absence of endothelin receptor antagonism, elevated ET-1 concentrations are strongly correlated with the severity and prognosis of these diseases.

Bosentan competes with the binding of ET-1 and other ET peptides to both ET_A and ET_B receptors, with a slightly higher affinity for ET_A receptors ($K_i = 4.1\text{--}43$ nanomolar) than for ET_B receptors ($K_i = 38\text{--}730$ nanomolar). Bosentan specifically antagonises ET receptors and does not bind to other receptors.

Efficacy

Animal models

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 in the lungs.

Efficacy in adult patients with pulmonary arterial hypertension

Two randomised, double-blind, multi-centre, placebo-controlled studies have been conducted in 32 (Study AC-052-351) and 213 (Study AC-052-352, BREATHE-1) adult patients with WHO functional class III–IV pulmonary arterial hypertension (primary pulmonary hypertension or pulmonary hypertension secondary mainly to scleroderma). After 4 weeks of Tracleer 62.5 mg twice daily, the maintenance doses studied in these studies were 125 mg twice daily in AC-052-351 and 125 mg twice daily and 250 mg twice daily in AC-052-352.

Tracleer was added to patients' current therapy, which could include a combination of anticoagulants, vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digoxin, but not epoprostenol. Control was placebo plus current therapy.

The primary endpoint for each study was change in 6-minute walk distance at 12 weeks for the first study and 16 weeks for the second study. In both studies, treatment with Tracleer resulted in significant increases in exercise capacity. The placebo-corrected increases in walk distance compared to baseline were 76 metres ($p = 0.02$; t-test) and 44 metres ($p = 0.0002$; Mann-Whitney U test) at the primary endpoint of each study, respectively. The differences between the two groups 125 mg twice daily and 250 mg twice daily were not statistically significant but there was a trend towards improved exercise capacity in the group treated with 250 mg twice daily.

The improvement in walk distance was apparent after 4 weeks of treatment, was clearly evident after 8 weeks of treatment and was maintained for up to 28 weeks of double-blind treatment in a subset of the patient population.

In a retrospective responder analysis based on change in walking distance, WHO functional class and dyspnoea of the 95 patients randomised to Tracleer 125 mg twice daily in the placebo-controlled studies, it was found that at week 8, 66 patients had improved, 22 were stable and 7 had deteriorated. Of the 22 patients stable at week 8, 6 improved at week 12/16 and 4 deteriorated compared with baseline. Of the 7 patients that deteriorated at week 8, 3 improved at week 12/16 and 4 deteriorated compared with baseline.

Invasive haemodynamic parameters were assessed in the first study only. Treatment with Tracleer led to a significant increase in cardiac index associated with a significant reduction in pulmonary artery pressure, pulmonary vascular resistance and mean right atrial pressure.

A reduction in symptoms of pulmonary arterial hypertension was observed with Tracleer treatment. Dyspnoea measurement during walk tests showed an improvement in Tracleer-treated patients. In the AC-052-352 study, 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%). The overall change in WHO functional class during both studies was significantly better among Tracleer-treated patients as compared with placebo-treated patients. Treatment with Tracleer was associated with a significant reduction in the rate of clinical worsening compared with placebo at 28 weeks (10.7% vs 37.1%, respectively; $p = 0.0015$).

In a randomised, double-blind, multi-centre, placebo-controlled study (AC-052-364; EARLY), 185 PAH patients in WHO functional class II (mean baseline 6-minute walk distance of 435 metres) 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 6 months. Enrolled patients were PAH-treatment-naïve ($n = 156$) or on a stable dose of sildenafil ($n = 29$). The co-primary endpoints were percentage change from baseline in PVR and change from baseline in 6-minute walk distance to Month 6 versus placebo. The table below illustrates the pre-specified protocol analyses.

	PVR (dyn.sec/cm⁵)		6-Minute Walk Distance (m)	
	Placebo ($n = 88$)	Bosentan ($n = 80$)	Placebo ($n = 91$)	Bosentan ($n = 86$)
Baseline (BL); mean (SD)	802 (365)	851 (535)	431 (92)	443 (83)
Change from BL; mean (SD)	128 (465)	-69 (475)	-8 (79)	11 (74)
Treatment effect	-22.6%		19	
95% CL	-34, -10		-4, 42	
P-value	< 0.0001		0.0758	

Treatment with bosentan was associated with a reduction in the rate of clinical worsening, defined as a composite of symptomatic progression, hospitalisation for PAH and death, compared with placebo (proportional risk reduction 77%, 95% CI 20%–94%, $p = 0.0114$). The treatment effect was driven by improvement in the component symptomatic progression. There was one hospitalisation related to PAH worsening in the bosentan group and 3 hospitalisations in the placebo group. Only one death occurred in each treatment group during the 6-month double-blind study period, therefore no conclusion can be drawn on survival.

In a prospective, multi-centre, randomized, double-blind, placebo-controlled study (BREATHE-5), patients with pulmonary arterial hypertension WHO functional Class III and Eisenmenger physiology associated with congenital heart disease received Tracleer 62.5 mg bid for 4 weeks, then 125 mg b.i.d. for a further 12 weeks ($n = 37$), or placebo ($n = 17$). The primary objective was to show that Tracleer did not worsen hypoxaemia. After 16 weeks, the mean oxygen saturation was increased in the bosentan group by 1.0% (95% CI -0.7; 2.8%) as compared to the placebo group, showing that bosentan did not worsen hypoxemia. The mean pulmonary vascular resistance was significantly reduced in the bosentan group (with a predominant effect observed in the subgroup of patients with bidirectional intracardiac shunt). After 16 weeks, the mean placebo-corrected increase in 6-minute walk distance was 53 meters ($p = 0.0079$) reflecting improvement of exercise capacity.

An open label, non-comparative study (AC-052-362; BREATHE-4) was performed in 16 patients with WHO Class III PAH associated with HIV infection. Patients were treated with Tracleer 62.5 mg bid for 4 weeks followed by 125 mg bid for a further 12 weeks. After 16 weeks treatment, there were significant improvements from baseline in exercise capacity: mean increase in 6-minute walk test: +91.4 meters from 332.6 meters on average at baseline ($p < 0.001$). No formal conclusion can be drawn regarding the effects of bosentan on antiretroviral drug efficacy (see also Section 4.4).

There are no studies to demonstrate beneficial effects on survival of treatment with Tracleer. However, long-term vital status was recorded for all 235 patients who were treated with bosentan in the two pivotal placebo-controlled studies (AC-052-351 and AC-052-352) and/or their two uncontrolled, open-label extensions. The mean duration of exposure to bosentan was 1.9 years \pm 0.7 years; [min: 0.1; max: 3.3 years] and patients were observed for a mean of 2.0 \pm 0.6 years. The majority of patients were diagnosed as PPH (72%) and were in WHO functional class III (84%). In this total population, Kaplan-Meier estimates of survival were 93% and 84% after 1 and 2 years after the start of treatment with Tracleer, respectively. Survival estimates were lower in the subgroup of patients with PAH secondary to systemic sclerosis. The estimates may have been influenced by the initiation of epoprostenol treatment in 43/235 patients.

Study performed in children with pulmonary arterial hypertension

One study has been conducted in children with pulmonary hypertension. Tracleer has been evaluated in an open-label non-controlled study in 19 paediatric patients with pulmonary arterial hypertension (AC-052-356, BREATHE-3: primary pulmonary hypertension 10 patients, and pulmonary arterial hypertension related to congenital heart diseases 9 patients). This study was primarily designed as a pharmacokinetic study (see section 5.2). Patients were divided into and dosed according to three body-weight groups (see section 4.2) for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. The age range was 3–15 years. Patients were in WHO functional class II (N = 15 patients, 79%) or class III (N = 4 patients, 21%) at baseline.

Haemodynamics were measured in 17 patients. The mean increase from baseline in cardiac index was 0.5 l/min/m², the mean decrease in mean pulmonary arterial pressure was 8 mmHg, and the mean decrease in pulmonary vascular resistance was 389 dyn·sec·cm⁻⁵. These haemodynamic improvements from baseline were similar with or without co-administration of epoprostenol. Changes in exercise test parameters at week 12 from baseline were highly variable and none were significant.

Combination 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 multi-centre, randomised, double-blind, parallel-group study 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-controlled study; 10 of the 19 paediatric patients were on concomitant Tracleer and epoprostenol therapy during the 12-week study. The safety profile of the combination was not different from the one expected with each component and the combination therapy was well tolerated in children and adults. The clinical benefit of the combination has not been demonstrated.

Systemic sclerosis with digital ulcer disease

Two randomised, double-blind, multi-centre, placebo-controlled studies have been conducted in 122 (Study AC-052-401, RAPIDS-1) and 190 (Study AC-052-331, RAPIDS-2) adult patients with systemic sclerosis and digital ulcer disease (either ongoing digital ulcers or a history of digital ulcers within the last year). In study AC-052-331, patients had to have at least one digital ulcer of recent onset, and across the two studies 85% of patients had ongoing digital ulcer disease at baseline. After 4 weeks of Tracleer 62.5 mg twice daily, the maintenance doses studied in both these studies were 125 mg twice daily. The duration of double-blind therapy was 16 weeks in study AC-052-401, and 24 weeks in study AC-052-331.

Background treatments for systemic sclerosis and digital ulcers were permitted if they remained constant for at least 1 month prior to the start of treatment and during the double-blind study period.

The number of new digital ulcers from baseline to study endpoint was a primary endpoint in both studies. Treatment with Tracleer resulted in fewer new digital ulcers for the duration of therapy, compared with placebo. In study AC-052-401, during 16 weeks of double-blind therapy, patients in the bosentan group developed a mean of 1.4 new digital ulcers vs. 2.7 new digital ulcers in the placebo group ($p = 0.0042$). In study AC-052-331, during 24 weeks of double-blind therapy, the corresponding figures were 1.9 vs. 2.7 new digital ulcers, respectively ($p = 0.0351$). In both studies, patients on bosentan were less likely to develop multiple new digital ulcers during the study and took longer to develop each successive new digital ulcer than did those on placebo. The effect of bosentan on reduction of the number of new digital ulcers was more pronounced in patients with multiple digital ulcers.

No effect of bosentan on time to healing of digital ulcers was observed in either study.

5.2 Pharmacokinetic properties

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.

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.

Absorption

In healthy subjects the absolute bioavailability of bosentan is approximately 50% and is not affected by food. The maximum plasma concentrations are attained within 3–5 hours.

Distribution

Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

A volume of distribution (V_{ss}) of about 18 litres was determined after an intravenous dose of 250 mg.

Biotransformation and elimination

After a single intravenous dose of 250 mg, the clearance was 8.2 l/h. The terminal elimination half-life ($t_{1/2}$) is 5.4 hours.

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 metabolising liver enzymes. Steady-state conditions are reached within 3–5 days.

Bosentan is eliminated by biliary excretion following metabolism in the liver by the cytochrome P450 isoenzymes, CYP2C9 and CYP3A4. Less than 3% of an administered oral dose is recovered in urine.

Bosentan forms three metabolites and only one of these is pharmacologically active. This metabolite is mainly excreted unchanged via the bile. In adult patients, the exposure to the active metabolite is greater than in healthy subjects. In patients with evidence of the presence of cholestasis, the exposure to the active metabolite may be increased.

Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19 and the P-glycoprotein. *In vitro*, bosentan inhibits the bile salt export pump in hepatocyte cultures.

In vitro data demonstrated that bosentan had no relevant inhibitory effect on the CYP isoenzymes tested (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4). Consequently, bosentan is not expected to increase the plasma concentrations of medicinal products metabolised by these isoenzymes.

Pharmacokinetics in special populations

Based on the investigated range of each variable, 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. No kinetic data are available in children under 2 years.

Children

The pharmacokinetics of single and multiple oral doses were studied in paediatric patients with pulmonary arterial hypertension who were dosed on the basis of body weight (see sections 5.1 BREATHE-3). 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 paediatric 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 with pulmonary arterial hypertension receiving 125 mg b.i.d. At steady state the systemic exposure in paediatric patients weighing 10–20 kg, 20–40 kg and > 40kg were 43%, 67% and 75%, respectively, of the adult systemic exposure.

In a second pharmacokinetics study (FUTURE 1), 36 paediatric patients aged 2–11 years with PAH were treated at 2 and 4 mg/kg b.i.d. with the dispersible tablet. No dose proportionality was observed. Steady-state bosentan plasma concentrations were similar at oral doses of 2 and 4 mg/kg. The AUC_τ was 3,577 ng·h/mL for 2 mg/kg b.i.d. and 3,371 ng·h/mL for 4 mg/kg b.i.d. Average exposure to bosentan in paediatric patients was about half the exposure in adult patients at 125 mg b.i.d. maintenance dose but showed large overlap with the findings in adults. Based on the findings in studies BREATHE-3 and FUTURE 1, it appears that the exposure to bosentan reaches a plateau at lower doses in paediatric patients than in adults, and that doses higher than 2 mg/kg b.i.d. will not result in greater exposure to bosentan in paediatric patients.

The consequences of these findings regarding hepatotoxicity are unknown. Gender and the concomitant use of intravenous epoprostenol had no significant effect on the pharmacokinetics of bosentan.

Hepatic impairment

In patients with mildly impaired liver function (Child-Pugh class A) no relevant changes in the pharmacokinetics have been observed. The steady state AUC of bosentan was 9% higher and the AUC of the active metabolite, Ro 48-5033, was 33% higher 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 Tracleer is contra-indicated in this patient population (see section 4.3).

Renal impairment

In patients with severe renal impairment (creatinine clearance 15–30 ml/min), plasma concentrations of bosentan decreased by approximately 10%. Plasma concentrations of bosentan metabolites increased about 2-fold in these patients as compared to subjects with normal renal function. No dose adjustment is required in patients with renal impairment. There is no specific clinical experience in patients undergoing dialysis. Based on physicochemical properties and the high degree of protein binding, bosentan is not expected to be removed from the circulation by dialysis to any significant extent (see section 4.2).

5.3 Preclinical safety data

A 2-year carcinogenicity study in mice showed an increased combined incidence of hepatocellular adenomas and carcinomas in males, but not in females, at plasma concentrations about 2 to 4 times the plasma concentrations achieved at the therapeutic dose in humans. 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 males, but not in females, at plasma concentrations about 9 to 14 times the plasma concentrations achieved at the therapeutic dose in humans. Bosentan was negative in tests for genotoxicity. There was evidence for a mild thyroid hormonal imbalance induced by bosentan in rats. However, there was no evidence of bosentan affecting thyroid function (thyroxine, TSH) in humans.

The effect of bosentan on mitochondrial function is unknown.

Bosentan has been shown to be teratogenic in rats at plasma levels higher than 1.5 times the plasma concentrations achieved at the therapeutic dose in humans. Teratogenic effects, including malformations of the head and face and of the major vessels, were dose dependent. The similarities of the pattern of malformations observed with other ET receptor antagonists and in ET knock-out mice indicate a class effect. Appropriate precautions must be taken for women of child-bearing potential (see sections 4.3, 4.4, 4.6).

In fertility studies in male and female rats at plasma concentrations 21 and 43 times, respectively, the expected therapeutic level in humans, no effects on sperm count, motility and viability, or on mating performance or fertility were observed, nor was there any adverse effect on the development of the pre-implantation embryo or on implantation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Maize starch
Pregelatinised starch
Sodium starch glycollate
Povidone
Glycerol dibehenate
Magnesium stearate

Film coat:

Hypromellose
Glycerol triacetate
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Ethylcellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PE/PVDC/aluminium-blisters containing 14 film-coated tablets.
Cartons contain 14, 56 or 112 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actelion Registration Ltd
BSI Building 13th Floor
389 Chiswick High Road
London W4 4AL
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/220/001
EU/1/02/220/002
EU/1/02/220/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 May 2002

Date of renewal: 15 May 2007

10. DATE OF REVISION OF THE TEXT

January 2010

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

Tracleer 125 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 125 mg bosentan (as monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablets):

Orange-white, oval, biconvex, film-coated tablets, embossed with "125" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:

- Primary (idiopathic and familial) PAH
- PAH secondary to scleroderma without significant interstitial pulmonary disease
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology

Some improvements have also been shown in patients with PAH WHO functional class II (see section 5.1).

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see section 5.1).

4.2 Posology and method of administration

Tablets are to be taken orally morning and evening, with or without food. The film-coated tablets are to be swallowed with water.

Pulmonary arterial hypertension

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

In adult patients, Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

For paediatric patients aged 2 years or older, the optimal maintenance dose has not been defined in well-controlled studies. However, pediatric pharmacokinetic data have shown that bosentan plasma concentrations in children were on average lower than in adult patients and were not increased by increasing the dose of Tracleer above 2 mg/kg twice daily (see section 5.2). Based on these pharmacokinetic results, higher doses are unlikely to be more effective, and greater adverse event rates cannot formally be excluded in young children if the dose is increased. No clinical study has been conducted to compare the efficacy/safety ratio of 2 mg/kg to 4 mg/kg twice daily in children.

There is only limited clinical experience in paediatric patients under 2 years of age.

In the case of clinical deterioration (e.g., decrease in 6-minute walk test distance by at least 10% compared with pre-treatment measurement) despite Tracleer treatment for at least 8 weeks (target dose for at least 4 weeks), alternative therapies should be considered. However, some patients who show no response after 8 weeks of treatment with Tracleer may respond favourably after an additional 4 to 8 weeks of treatment.

In the case of late clinical deterioration despite treatment with Tracleer (i.e., after several months of treatment), the treatment should be re-assessed. Some patients not responding well to 125 mg twice daily of Tracleer may slightly improve their exercise capacity when the dose is increased to 250 mg twice daily. A careful risk/benefit assessment should be made, taking into consideration that the liver toxicity is dose dependent (see sections 4.4 and 5.1).

Discontinuation of treatment

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. However, to avoid the possible occurrence of harmful clinical deterioration due to potential rebound effect, gradual dose reduction (halving the dose for 3 to 7 days) should be considered. Intensified monitoring is recommended during the discontinuation period. If the decision to withdraw Tracleer is taken, it should be done gradually while an alternative therapy is introduced.

Systemic sclerosis with ongoing digital ulcer disease

Treatment should only be initiated and monitored by a physician experienced in the treatment of systemic sclerosis.

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

Controlled clinical study experience in this indication is limited to 6 months (see section 5.1).

The patient's response to treatment and need for continued therapy should be re-evaluated on a regular basis. A careful risk/benefit assessment should be made, taking into consideration the liver toxicity of bosentan (see sections 4.4 and 4.8).

There are no data on the safety and efficacy in patients under the age of 18 years. Kinetic data are not available for Tracleer in young children with this disease.

Special populations

Dosage in hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment (i.e., Child-Pugh class A) (see section 5.2). Tracleer is contraindicated in patients with moderate to severe liver dysfunction (see sections 4.3, 4.4 and 5.2).

Dosage in renal impairment

No dose adjustment is required in patients with renal impairment. No dose adjustment is required in patients undergoing dialysis (see section 5.2).

Dosage in elderly patients

No dose adjustment is required in patients over the age of 65 years.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients

- Moderate to severe hepatic impairment , i.e. Child-Pugh Class B or C (see section 5.2)
- Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal (see section 4.4)
- Concomitant use of cyclosporine A (see section 4.5)
- Pregnancy (see section 4.4 and 4.6)
- Women of childbearing potential who are not using reliable methods of contraception (see sections 4.4, 4.5 and 4.6)

4.4 Special warnings and precautions for use

The efficacy of Tracleer has not been established in patients with severe pulmonary arterial hypertension. Transfer to a therapy that is recommended at the severe stage of the disease (e.g., epoprostenol) should be considered if the clinical condition deteriorates (see section 4.2).

The benefit/risk balance of bosentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension.

Tracleer should only be initiated if the systemic systolic blood pressure is higher than 85 mmHg.

Tracleer has not been shown to have a beneficial effect on the healing of existing digital ulcers.

Liver function

Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment but may also occur late in treatment (see section 4.8). These increases may be partly due to competitive inhibition of the elimination of bile salts from hepatocytes but other mechanisms, which have not been clearly established, are probably also involved in the occurrence of liver dysfunction. The accumulation of bosentan in hepatocytes leading to cytolysis with potentially severe damage of the liver, or an immunological mechanism, are not excluded. Liver dysfunction risk may also be increased when medicinal products that are inhibitors of the bile salt export pump (BSEP), e.g., rifampicin, glibenclamide and cyclosporine A (see sections 4.3 and 4.5), are co-administered with bosentan, but limited data are available.

Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Tracleer. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase.

Recommendations in case of ALT/AST elevations

ALT/AST levels	Treatment and monitoring recommendations
> 3 and $\leq 5 \times$ ULN	Confirm by another liver test; if confirmed, reduce the daily dose or stop treatment (see section 4.2), monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider continuing or re-introducing Tracleer according to the conditions described below.
> 5 and $\leq 8 \times$ ULN	Confirm by another liver test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider re-introducing Tracleer according to the conditions described below.
> 8 \times ULN	Treatment must be stopped and re-introduction of Tracleer is not to be considered.

In case of associated clinical symptoms of liver injury, i.e., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), treatment must be stopped and re-introduction of Tracleer is not to be considered.

Re-introduction of treatment

Re-introduction of treatment with Tracleer should only be considered if the potential benefits of treatment with Tracleer outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the guidelines detailed in section 4.2. **Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.**

ULN= Upper Limit of Normal

Haemoglobin concentration

Treatment with bosentan has been associated with dose-related decreases in haemoglobin concentration (see section 4.8). In placebo-controlled studies, bosentan-related decreases in haemoglobin concentration were not progressive, and stabilised after the first 4–12 weeks of treatment. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first 4 months, and quarterly thereafter. If a clinically relevant decrease in haemoglobin concentration occurs, further evaluation and investigation should be undertaken to determine the cause and need for specific treatment. In the post-marketing period, cases of anaemia requiring red blood cell transfusion have been reported (see section 4.8).

Women of child-bearing potential

Tracleer treatment must not be initiated in women of child-bearing potential unless they practice reliable contraception (see section 4.5) and the result of the pre-treatment pregnancy test is negative (see section 4.6).

Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods 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 section 4.5). Therefore, women of child-bearing 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 gynaecologist 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.

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema 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 oedema in patients treated with Tracleer who had a suspected diagnosis of pulmonary veno-occlusive disease.

Pulmonary arterial hypertension patients with concomitant left ventricular failure

No specific study has been performed in patients with pulmonary hypertension and concomitant left ventricular dysfunction. However, 1,611 patients (804 Tracleer- and 807 placebo-treated patients) with

severe chronic heart failure (CHF) were treated for a mean duration of 1.5 years in a placebo-controlled study (study AC-052-301/302 [ENABLE 1 & 2]). In this study there was an increased incidence of hospitalisation due to CHF during the first 4 - 8 weeks of treatment with Tracleer, which could have been the result of fluid retention. In this study, fluid retention was manifested by early weight gain, decreased haemoglobin concentration and increased incidence of leg oedema. At the end of this study, there was no difference in overall hospitalisations for heart failure nor in mortality between Tracleer- and placebo-treated patients. Consequently, it is recommended that patients be monitored for signs of fluid retention (e.g., weight gain), especially if they concomitantly suffer from severe systolic dysfunction. Should this occur, starting treatment with diuretics is recommended, or the dose of existing diuretics should be increased. Treatment with diuretics should be considered in patients with evidence of fluid retention before the start of treatment with Tracleer.

Pulmonary arterial hypertension associated with HIV infection

There is limited clinical study experience with the use of Tracleer in patients with PAH associated with HIV infection, treated with antiretroviral medicinal products (see section 5.1). An interaction study between bosentan and lopinavir+ritonavir in healthy subjects showed increased plasma concentrations of bosentan with the maximum level during the first 4 days of treatment (see section 4.5). When treatment with Tracleer is initiated in patients who require ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be closely monitored with special attention, at the beginning of the initiation phase, to the risk of hypotension and to liver function tests. An increased long-term risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. Due to the potential for interactions related to the inducing effect of bosentan on CYP450 (see section 4.5), which could affect the efficacy of antiretroviral therapy, these patients should also be monitored carefully regarding their HIV infection.

Concomitant use with other medicinal products

Glibenclamide: Tracleer should not be used concomitantly with glibenclamide, due to an increased risk of elevated liver aminotransferases (see section 4.5). An alternative antidiabetic medicinal product should be used in patients in whom an antidiabetic treatment is indicated.

Fluconazole: concomitant use of Tracleer with fluconazole is not recommended (see section 4.5). Although not studied, this combination may lead to large increases in plasma concentrations of bosentan.

Rifampicin: co-administration of Tracleer with rifampicin is not recommended (see section 4.5).

Concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor should be avoided (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

Bosentan is an inducer of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4. *In vitro* data also suggest an induction of CYP2C19. Consequently, plasma concentrations of substances metabolised by these isoenzymes will be decreased when Tracleer is co-administered. The possibility of altered efficacy of medicinal products metabolised 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 is metabolised by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been studied. The combination should be used with caution. Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor

(such as ketoconazole, itraconazole and ritonavir) and a CYP2C9 inhibitor (such as voriconazole) with Tracleer is not recommended.

Specific interaction studies have demonstrated the following:

Cyclosporine A: co-administration of Tracleer and cyclosporine A (a calcineurin inhibitor) is contraindicated (see section 4.3). Indeed, when co-administered, initial trough concentrations of bosentan were approximately 30-fold higher than those measured after bosentan alone. At steady state, bosentan plasma concentrations were 3- to 4-fold higher than with bosentan alone. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. The blood concentrations of cyclosporine A (a CYP3A4 substrate) decreased by approximately 50%. This is most likely due to induction of CYP3A4 by bosentan.

Tacrolimus, sirolimus: co-administration of tacrolimus or sirolimus and Tracleer has not been studied in man but co-administration of tacrolimus or sirolimus and Tracleer may result in increased plasma concentrations of bosentan in analogy to co-administration with cyclosporine A. Concomitant Tracleer may reduce the plasma concentrations of tacrolimus and sirolimus. Therefore, concomitant use of Tracleer and tacrolimus or sirolimus is not advisable. Patients in need of the combination should be closely monitored for adverse events related to Tracleer and for tacrolimus and sirolimus blood concentrations.

Glibenclamide: co-administration of Tracleer 125 mg twice daily for 5 days decreased the plasma concentrations of glibenclamide (a CYP3A4 substrate) by 40%, with potential significant decrease of the hypoglycaemic effect. The plasma concentrations of bosentan were also decreased by 29%. In addition, an increased incidence of elevated aminotransferases was observed in patients receiving concomitant therapy. Both glibenclamide and bosentan inhibit the bile salt export pump, which could explain the elevated aminotransferases. In this context, this combination should not be used (see section 4.4). No drug-drug interaction data are available with the other sulfonylureas.

Hormonal contraceptives: Co-administration of Tracleer 125 mg twice daily for 7 days with a single dose of oral contraceptive containing norethisterone 1 mg + ethinyl estradiol 35 mcg decreased the AUC of norethisterone and ethinyl estradiol by 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, 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 sections 4.4, 4.6).

Warfarin: co-administration of bosentan 500 mg twice daily for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29% and 38%, respectively. Clinical experience of concomitant administration of bosentan with warfarin in patients with pulmonary arterial hypertension did not result in clinically relevant changes in International Normalized Ratio (INR) or warfarin dose (baseline versus end of the clinical studies). In addition, the frequency of changes in warfarin dose during the studies due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. No dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated but intensified monitoring of INR is recommended, especially during bosentan initiation and the up-titration period.

Simvastatin: co-administration of Tracleer 125 mg twice daily for 5 days decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β -hydroxy acid metabolite by 34% and 46%, respectively. The plasma concentrations of bosentan were not affected by concomitant simvastatin. Monitoring of cholesterol levels and subsequent dosage adjustment should be considered.

Ketoconazole: co-administration of Tracleer 62.5 mg twice daily for 6 days and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan approximately 2-fold. No dose adjustment of Tracleer is considered necessary. Although not demonstrated through *in vivo* studies, similar increases in bosentan plasma concentrations are expected with the other potent CYP3A4 inhibitors (such as itraconazole and ritonavir). However, when combined with a CYP3A4 inhibitor,

patients who are poor metabolisers of CYP2C9 are at risk of increases in bosentan plasma concentrations that may be of higher magnitude, thus leading to potential harmful adverse events.

Rifampicin: co-administration in 9 healthy subjects of Tracleer 125 mg twice daily for 7 days and rifampicin, a potent inducer of CYP2C9 and CYP3A4, decreased the plasma concentrations of bosentan by 58%, and this decrease could achieve almost 90% in an individual case. A subsequent significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. Data on other CYP3A4 inducers, e.g. carbamazepine, phenobarbital, phenytoin and St. John's wort are lacking, but their concomitant administration is expected to lead to reduced systemic exposure to bosentan. A clinically significant reduction of efficacy cannot be excluded.

Epoprostenol: limited data obtained from a study (AC-052-356, BREATHE-3) in which 10 paediatric patients received the combination of Tracleer and epoprostenol indicate 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 section 5.1).

Sildenafil: co-administration of Tracleer 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease of the sildenafil AUC and a 50% increase of the bosentan AUC. Caution is recommended in case of co-administration.

Digoxin: co-administration of bosentan 500 mg twice daily for 7 days decreased the AUC, C_{max} and C_{min} of digoxin by 12%, 9% and 23%, respectively. The mechanism for this interaction may be induction of P-glycoprotein. This interaction is unlikely to be of clinical relevance.

Antiretroviral agents :

Lopinavir+Ritonavir (and other boosted protease inhibitors): Co-administration of Tracleer 125 mg twice daily and lopinavir+ritonavir 400+100mg twice daily during 9.5 days in healthy volunteers, resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after Tracleer administered alone. On day 9, plasma concentrations of bosentan were approximately 5-fold higher 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. When administered concomitantly with lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be monitored.

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. Appropriate monitoring of the HIV therapy is recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors (see section 4.4.).

Other antiretroviral agents:

No specific recommendation can be made with regard to other available antiretroviral agents due to the lack of data. It is emphasized that due to a marked hepatotoxicity of nevirapine that could cumulate with bosentan liver toxicity, this combination is not recommended.

4.6 Pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (teratogenicity, embryotoxicity, see section 5.3). There are no reliable data on the use of Tracleer in pregnant women. The potential risk for humans is still unknown. Tracleer is contraindicated in pregnancy (see section 4.3).

Use in women of child-bearing potential

Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods 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 section 4.5). Therefore, women of childbearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but must 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 gynaecologist 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.

Use during lactation

It is not known whether bosentan is excreted into human breast milk. Breast-feeding is not recommended during treatment with Tracleer.

4.7 Effects on ability to drive and use machines

No studies on the effect of Tracleer on the ability to drive and use machines have been performed. Tracleer may cause dizziness, which could influence the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions

Integrated findings from placebo-controlled studies

In eight placebo-controlled studies, six of which were for indications other than pulmonary arterial hypertension, a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The foreseen duration of treatment ranged from 2 weeks to 6 months. The adverse drug reactions that occurred more frequently on bosentan than on placebo ($\geq 3\%$ of bosentan-treated patients, with $\geq 2\%$ difference) were headache (15.8% vs 12.8%), flushing (6.6% vs 1.7%), abnormal hepatic function (5.9% vs 2.1%), leg oedema (4.7% vs 1.4%), and anaemia (3.4% vs 1.0%), all of which were dose related.

Adverse reactions/undesirable effects are ranked according to frequency using the following convention : Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Frequency categories do not account for other factors, including varying study duration, pre-existing conditions, and baseline patient characteristics. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Placebo-controlled studies in primary (idiopathic/familial) PAH and PAH associated with connective tissue diseases

The table below shows the adverse drug reactions, defined as adverse events reported in $\geq 3\%$ of patients and more frequently on bosentan (125 and 250 mg twice daily) in three placebo-controlled trials (bosentan n = 258, placebo n = 172) in PAH.

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection, Nasopharyngitis,

		Respiratory tract infection, Sinusitis
Blood and lymphatic system disorders	Common	Anaemia
Nervous system disorders	Very common Common	Headache ¹ Syncope
Cardiac disorders	Common	Palpitations
Vascular disorders	Common	Hypotension, Flushing,
Hepatobiliary disorders	Very common	Liver function test abnormal
Musculoskeletal and connective tissue disorder	Common	Arthralgia
General disorders and administration site conditions	Very common Common	Oedema ² , Fluid retention Chest pain

¹ Headache was reported in 15.1% of patients on bosentan and 14.5% of patients on placebo.

² Oedema or fluid retention was reported in 11.6% of patients on bosentan and 9.9% of patients on placebo.

Treatment discontinuations due to adverse events, during the clinical studies in patients with pulmonary arterial hypertension, at doses of 125 and 250 mg twice daily, occurred with the same frequency (5.8%) in bosentan and placebo-treated patients.

Placebo-controlled study in PAH associated with congenital heart disease (BREATHE-5)

The safety profile of Tracleer in this population was similar to that observed in the pivotal studies in patients with PAH. Adverse events that occurred in a greater proportion of patients on Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily (n = 37) than on placebo (n = 17) included peripheral oedema (18.9% vs. 5.9%), headache (13.5% vs. 11.8%), palpitations (10.8% vs. 0%), dizziness (8.1% vs. 5.9%) and chest pain (8.1% vs. 0%). Four patients discontinued due to adverse events, two (5.4%) in the bosentan group and two (11.8%) in the placebo group.

Uncontrolled study in patients with PAH associated with HIV infection (BREATHE-4)

The safety profile in this population (n = 16) when treated with Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily was similar to that observed in the pivotal studies in patients with PAH. The most frequent adverse events were peripheral oedema (31%), headache (19%), abnormal liver function (13%), muscle cramps (13%), fluid retention (13%) and vomiting (13%). Haematological abnormalities (anaemia and decrease in neutrophil count) were observed in some patients (see section 4.4).

Uncontrolled trials in paediatric patients (BREATHE-3; FUTURE 1)

The safety profile in this population (BREATHE-3: n = 19, Tracleer 2 mg/kg twice daily; treatment duration 12 weeks; FUTURE 1: n = 36, Tracleer 2 mg/kg twice daily for 4 weeks followed by 4 mg/kg twice daily; treatment duration 12 weeks) was similar to that observed in the pivotal trials in adult patients with PAH. In BREATHE-3, the most frequent adverse events were flushing (21%), headache, and abnormal hepatic function (each 16%). In FUTURE-1, the most frequent adverse events were infections (33%) and abdominal pain/discomfort (19%). There were no cases of liver enzyme elevations in the FUTURE-1 study.

Placebo-controlled studies in digital ulcers

The table below shows the adverse drug reactions, defined as adverse events reported in $\geq 3\%$ of patients and more frequently on bosentan (125 mg twice daily) in the two pivotal placebo-controlled studies in digital ulcers (bosentan n = 175, placebo n = 133).

System organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Infected skin ulcer, Urinary tract

		infection
Blood and lymphatic system disorders	Common	Anaemia, Haemoglobin decrease
Vascular disorders	Common	Flushing
Gastrointestinal disorders	Common	Gastrooesophageal reflux disease, Diarrhoea, Abdominal pain, Constipation
Hepatobiliary disorders	Very common	Liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Erythema
Musculoskeletal and connective tissue disorder	Common	Pain in extremity, Back pain
General disorders and administration site conditions	Very common	Oedema, Fluid retention

Laboratory abnormalities

Liver test abnormalities

Bosentan has been associated with dose-related elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases. In the clinical programme, liver enzyme changes generally occurred within the first 26 weeks of treatment, usually developed gradually, and were mainly asymptomatic. They returned, in all cases during the clinical programme, to pre-treatment levels, without sequelae, within a few days to 9 weeks either spontaneously or after dose reduction or discontinuation. In the post-marketing period rare cases of liver cirrhosis and liver failure have been reported (see end of section 4.8).

The mechanism of this adverse effect is unclear. These elevations in aminotransferases may reverse spontaneously while continuing treatment with the maintenance dose of Tracleer or after dose reduction, but interruption or cessation may be necessary (see section 4.4).

In the eight integrated placebo-controlled studies, six of which were for indications other than pulmonary arterial hypertension, elevations in liver aminotransferases by greater than 3 times the upper limit of normal (ULN) were observed in 11.2% of the bosentan-treated patients as compared to 1.8% of the placebo-treated patients. Bilirubin increases to $> 3 \times$ ULN were associated with aminotransferase increases ($> 3 \times$ ULN) in 2 of 658 (0.3%) of patients treated with bosentan. Nine of the 74 bosentan-treated patients who had elevated liver aminotransferases ($> 3 \times$ ULN) also had symptoms such as abdominal pain, nausea/vomiting, and fever.

In studies in patients with pulmonary arterial hypertension, the incidence of elevated liver aminotransferases ($> 3 \times$ ULN) was 12.8% in bosentan-treated patients (N = 257), 12.3% in patients treated with 125 mg twice daily and 14.3% in patients treated with 250 mg twice daily. Eight-fold increases were seen in 3.7% of pulmonary arterial hypertension patients on 125 mg twice daily and 7.1% of pulmonary arterial hypertension patients on 250 mg twice daily.

In the two studies in patients with digital ulcers the incidence of elevated liver aminotransferases ($> 3 \times$ ULN) was 11.3% in bosentan-treated patients (N = 168) compared with 0.8% in placebo-treated patients (N = 129). Elevations to $> 8 \times$ ULN were seen in 2.4% of bosentan-treated patients with digital ulcers.

Haemoglobin

The mean decrease in haemoglobin concentration from baseline to study completion for the bosentan-treated patients was 0.9 g/dl and for the placebo-treated patients was 0.1 g/dl.

In eight placebo-controlled studies, clinically relevant decreases in haemoglobin (> 15% decrease from baseline resulting in values < 11 g/dl) were observed in 5.6% of bosentan-treated patients as compared with 2.6% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg twice daily, clinically relevant decreases in haemoglobin occurred in 3.0% and 1.3% of the bosentan- and placebo-treated patients, respectively.

In the two studies in patients with digital ulcers, clinically relevant decreases in haemoglobin (decrease from baseline resulting in haemoglobin values < 10 g/dL) were observed in 4.2% of bosentan-treated patients (N = 167), compared with 3.1% of placebo-treated patients (N = 129).

In the post-marketing period cases of anaemia requiring red blood cell transfusion have been reported (see end of section 4.8).

Postmarketing experience

The majority of adverse events reported during the post-marketing period have been similar to those reported in clinical studies.

Undesirable effects are ranked under headings of frequency using the following convention; very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$).

Gastrointestinal disorders:

Common: nausea

Uncommon: vomiting, abdominal pain, diarrhoea

Hepato-biliary disorders:

Uncommon: aminotransferase elevations associated with hepatitis and/or jaundice

Rare: liver cirrhosis, liver failure

Skin and subcutaneous tissue disorders:

Uncommon: hypersensitivity reactions including dermatitis, pruritus and rash

Immune system disorders:

Rare: anaphylaxis and/or angioedema

Blood and lymphatic system disorders:

Common: anaemia or haemoglobin decreases, sometimes requiring red blood cell transfusion (see section 4.4)

Uncommon: thrombocytopenia

Rare: neutropenia, leukopenia

In the post-marketing period rare cases of unexplained hepatic cirrhosis were reported after prolonged therapy with Tracleer in patients with multiple co-morbidities and therapies with medicinal products. There have also been rare reports of liver failure. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with Tracleer (see section 4.4).

4.9 Overdose

Bosentan has been administered as a single dose of up to 2400 mg to healthy subjects and up to 2000 mg/day for 2 months in patients with a disease other than pulmonary hypertension. The most common adverse event was headache of mild to moderate intensity.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antihypertensives, ATC code: C02KX01

Mechanism of action

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (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-1 (ET-1) is one of the most potent vasoconstrictors known and can also promote fibrosis, cell proliferation, cardiac hypertrophy, and remodeling and is pro-inflammatory. These effects are mediated by endothelin binding to ET_A and ET_B receptors located in the endothelium and vascular smooth muscle cells. ET-1 concentrations in tissues and plasma are increased in several cardiovascular disorders and connective tissue diseases, including pulmonary arterial hypertension, scleroderma, acute and chronic heart failure, myocardial ischaemia, systemic hypertension and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In pulmonary arterial hypertension and heart failure, in the absence of endothelin receptor antagonism, elevated ET-1 concentrations are strongly correlated with the severity and prognosis of these diseases.

Bosentan competes with the binding of ET-1 and other ET peptides to both ET_A and ET_B receptors, with a slightly higher affinity for ET_A receptors ($K_i = 4.1\text{--}43$ nanomolar) than for ET_B receptors ($K_i = 38\text{--}730$ nanomolar). Bosentan specifically antagonises ET receptors and does not bind to other receptors.

Efficacy

Animal models

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 in the lungs.

Efficacy in adult patients with pulmonary arterial hypertension

Two randomised, double-blind, multi-centre, placebo-controlled studies have been conducted in 32 (Study AC-052-351) and 213 (Study AC-052-352, BREATHE-1) adult patients with WHO functional class III–IV pulmonary arterial hypertension (primary pulmonary hypertension or pulmonary hypertension secondary mainly to scleroderma). After 4 weeks of Tracleer 62.5 mg twice daily, the maintenance doses studied in these studies were 125 mg twice daily in AC-052-351 and 125 mg twice daily and 250 mg twice daily in AC-052-352.

Tracleer was added to patients' current therapy, which could include a combination of anticoagulants, vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digoxin, but not epoprostenol. Control was placebo plus current therapy.

The primary endpoint for each study was change in 6-minute walk distance at 12 weeks for the first study and 16 weeks for the second study. In both studies, treatment with Tracleer resulted in significant increases in exercise capacity. The placebo-corrected increases in walk distance compared to baseline were 76 metres ($p = 0.02$; t-test) and 44 metres ($p = 0.0002$; Mann-Whitney U test) at the primary endpoint of each study, respectively. The differences between the two groups 125 mg twice daily and 250 mg twice daily were not statistically significant but there was a trend towards improved exercise capacity in the group treated with 250 mg twice daily.

The improvement in walk distance was apparent after 4 weeks of treatment, was clearly evident after 8 weeks of treatment and was maintained for up to 28 weeks of double-blind treatment in a subset of the patient population.

In a retrospective responder analysis based on change in walking distance, WHO functional class and dyspnoea of the 95 patients randomised to Tracleer 125 mg twice daily in the placebo-controlled studies, it was found that at week 8, 66 patients had improved, 22 were stable and 7 had deteriorated. Of the 22 patients stable at week 8, 6 improved at week 12/16 and 4 deteriorated compared with baseline. Of the 7 patients that deteriorated at week 8, 3 improved at week 12/16 and 4 deteriorated compared with baseline.

Invasive haemodynamic parameters were assessed in the first study only. Treatment with Tracleer led to a significant increase in cardiac index associated with a significant reduction in pulmonary artery pressure, pulmonary vascular resistance and mean right atrial pressure.

A reduction in symptoms of pulmonary arterial hypertension was observed with Tracleer treatment. Dyspnoea measurement during walk tests showed an improvement in Tracleer-treated patients. In the AC-052-352 study, 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%). The overall change in WHO functional class during both studies was significantly better among Tracleer-treated patients as compared with placebo-treated patients. Treatment with Tracleer was associated with a significant reduction in the rate of clinical worsening compared with placebo at 28 weeks (10.7% vs 37.1%, respectively; $p = 0.0015$).

In a randomised, double-blind, multi-centre, placebo-controlled study (AC-052-364; EARLY), 185 PAH patients in WHO functional class II (mean baseline 6-minute walk distance of 435 metres) 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 6 months. Enrolled patients were PAH-treatment-naïve ($n = 156$) or on a stable dose of sildenafil ($n = 29$). The co-primary endpoints were percentage change from baseline in PVR and change from baseline in 6-minute walk distance to Month 6 versus placebo. The table below illustrates the pre-specified protocol analyses.

	PVR (dyn.sec/cm⁵)		6-Minute Walk Distance (m)	
	Placebo (n =88)	Bosentan (n=80)	Placebo (n=91)	Bosentan (n=86)
Baseline (BL); mean (SD)	802 (365)	851 (535)	431 (92)	443 (83)
Change from BL; mean (SD)	128 (465)	-69 (475)	-8 (79)	11 (74)
Treatment effect	-22.6%		19	
95% CL	-34, -10		-4, 42	
P-value	< 0.0001		0.0758	

Treatment with bosentan was associated with a reduction in the rate of clinical worsening, defined as a composite of symptomatic progression, hospitalisation for PAH and death, compared with placebo (proportional risk reduction 77%, 95% CI 20%–94%, $p = 0.0114$). The treatment effect was driven by improvement in the component symptomatic progression. There was one hospitalisation related to PAH worsening in the bosentan group and 3 hospitalisations in the placebo group. Only one death occurred in each treatment group during the 6-month double-blind study period, therefore no conclusion can be drawn on survival.

In a prospective, multi-centre, randomized, double-blind, placebo-controlled study (BREATHE-5), patients with pulmonary arterial hypertension WHO functional Class III and Eisenmenger physiology associated with congenital heart disease received Tracleer 62.5 mg bid for 4 weeks, then 125 mg b.i.d. for a further 12 weeks ($n = 37$), or placebo ($n = 17$). The primary objective was to show that Tracleer did not worsen hypoxaemia. After 16 weeks, the mean oxygen saturation was increased in the bosentan group by 1.0% (95% CI -0.7; 2.8%) as compared to the placebo group, showing that bosentan did not worsen hypoxemia. The mean pulmonary vascular resistance was significantly reduced in the bosentan group (with a predominant effect observed in the subgroup of patients with bidirectional intracardiac shunt). After 16 weeks, the mean placebo-corrected increase in 6-minute walk distance was 53 meters ($p = 0.0079$) reflecting improvement of exercise capacity.

An open label, non-comparative study (AC-052-362; BREATHE-4) was performed in 16 patients with WHO Class III PAH associated with HIV infection. Patients were treated with Tracleer 62.5 mg bid for 4 weeks followed by 125 mg bid for a further 12 weeks. After 16 weeks treatment, there were significant improvements from baseline in exercise capacity: mean increase in 6-minute walk test: +91.4 meters from 332.6 meters on average at baseline ($p < 0.001$). No formal conclusion can be drawn regarding the effects of bosentan on antiretroviral drug efficacy (see also Section 4.4).

There are no studies to demonstrate beneficial effects on survival of treatment with Tracleer. However, long-term vital status was recorded for all 235 patients who were treated with bosentan in the two pivotal placebo-controlled studies (AC-052-351 and AC-052-352) and/or their two uncontrolled, open-label extensions. The mean duration of exposure to bosentan was 1.9 years \pm 0.7 years; [min: 0.1; max: 3.3 years] and patients were observed for a mean of 2.0 \pm 0.6 years. The majority of patients were diagnosed as PPH (72%) and were in WHO functional class III (84%). In this total population, Kaplan-Meier estimates of survival were 93% and 84% after 1 and 2 years after the start of treatment with Tracleer, respectively. Survival estimates were lower in the subgroup of patients with PAH secondary to systemic sclerosis. The estimates may have been influenced by the initiation of epoprostenol treatment in 43/235 patients.

Study performed in children with pulmonary arterial hypertension

One study has been conducted in children with pulmonary hypertension. Tracleer has been evaluated in an open-label non-controlled study in 19 paediatric patients with pulmonary arterial hypertension (AC-052-356, BREATHE-3: primary pulmonary hypertension 10 patients, and pulmonary arterial hypertension related to congenital heart diseases 9 patients). This study was primarily designed as a pharmacokinetic study (see section 5.2). Patients were divided into and dosed according to three body-weight groups (see section 4.2) for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. The age range was 3–15 years. Patients were in WHO functional class II (N = 15 patients, 79%) or class III (N = 4 patients, 21%) at baseline.

Haemodynamics were measured in 17 patients. The mean increase from baseline in cardiac index was 0.5 l/min/m², the mean decrease in mean pulmonary arterial pressure was 8 mmHg, and the mean decrease in pulmonary vascular resistance was 389 dyn·sec·cm⁻⁵. These haemodynamic improvements from baseline were similar with or without co-administration of epoprostenol. Changes in exercise test parameters at week 12 from baseline were highly variable and none were significant.

Combination 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 multi-centre, randomised, double-blind, parallel-group study 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-controlled study; 10 of the 19 paediatric patients were on concomitant Tracleer and epoprostenol therapy during the 12-week study. The safety profile of the combination was not different from the one expected with each component and the combination therapy was well tolerated in children and adults. The clinical benefit of the combination has not been demonstrated.

Systemic sclerosis with digital ulcer disease

Two randomised, double-blind, multi-centre, placebo-controlled studies have been conducted in 122 (Study AC-052-401, RAPIDS-1) and 190 (Study AC-052-331, RAPIDS-2) adult patients with systemic sclerosis and digital ulcer disease (either ongoing digital ulcers or a history of digital ulcers within the last year). In study AC-052-331, patients had to have at least one digital ulcer of recent onset, and across the two studies 85% of patients had ongoing digital ulcer disease at baseline. After 4 weeks of Tracleer 62.5 mg twice daily, the maintenance doses studied in both these studies were 125 mg twice daily. The duration of double-blind therapy was 16 weeks in study AC-052-401, and 24 weeks in study AC-052-331.

Background treatments for systemic sclerosis and digital ulcers were permitted if they remained constant for at least 1 month prior to the start of treatment and during the double-blind study period.

The number of new digital ulcers from baseline to study endpoint was a primary endpoint in both studies. Treatment with Tracleer resulted in fewer new digital ulcers for the duration of therapy, compared with placebo. In study AC-052-401, during 16 weeks of double-blind therapy, patients in the bosentan group developed a mean of 1.4 new digital ulcers vs. 2.7 new digital ulcers in the placebo group ($p = 0.0042$). In study AC-052-331, during 24 weeks of double-blind therapy, the corresponding figures were 1.9 vs. 2.7 new digital ulcers, respectively ($p = 0.0351$). In both studies, patients on bosentan were less likely to develop multiple new digital ulcers during the study and took longer to develop each successive new digital ulcer than did those on placebo. The effect of bosentan on reduction of the number of new digital ulcers was more pronounced in patients with multiple digital ulcers.

No effect of bosentan on time to healing of digital ulcers was observed in either study.

5.2 Pharmacokinetic properties

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.

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.

Absorption

In healthy subjects the absolute bioavailability of bosentan is approximately 50% and is not affected by food. The maximum plasma concentrations are attained within 3–5 hours.

Distribution

Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

A volume of distribution (V_{ss}) of about 18 litres was determined after an intravenous dose of 250 mg.

Biotransformation and elimination

After a single intravenous dose of 250 mg, the clearance was 8.2 l/h. The terminal elimination half-life ($t_{1/2}$) is 5.4 hours.

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 metabolising liver enzymes. Steady-state conditions are reached within 3–5 days.

Bosentan is eliminated by biliary excretion following metabolism in the liver by the cytochrome P450 isoenzymes, CYP2C9 and CYP3A4. Less than 3% of an administered oral dose is recovered in urine.

Bosentan forms three metabolites and only one of these is pharmacologically active. This metabolite is mainly excreted unchanged via the bile. In adult patients, the exposure to the active metabolite is greater than in healthy subjects. In patients with evidence of the presence of cholestasis, the exposure to the active metabolite may be increased.

Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19 and the P-glycoprotein. *In vitro*, bosentan inhibits the bile salt export pump in hepatocyte cultures.

In vitro data demonstrated that bosentan had no relevant inhibitory effect on the CYP isoenzymes tested (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4). Consequently, bosentan is not expected to increase the plasma concentrations of medicinal products metabolised by these isoenzymes.

Pharmacokinetics in special populations

Based on the investigated range of each variable, 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. No kinetic data are available in children under 2 years.

Children

The pharmacokinetics of single and multiple oral doses were studied in paediatric patients with pulmonary arterial hypertension who were dosed on the basis of body weight (see sections 5.1 BREATHE-3). 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 paediatric 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 with pulmonary arterial hypertension receiving 125 mg b.i.d. At steady state the systemic exposure in paediatric patients weighing 10–20 kg, 20–40 kg and > 40kg were 43%, 67% and 75%, respectively, of the adult systemic exposure.

In a second pharmacokinetics study (FUTURE 1), 36 paediatric patients aged 2–11 years with PAH were treated at 2 and 4 mg/kg b.i.d. with the dispersible tablet. No dose proportionality was observed. Steady-state bosentan plasma concentrations were similar at oral doses of 2 and 4 mg/kg. The AUC_τ was 3,577 ng·h/mL for 2 mg/kg b.i.d. and 3,371 ng·h/mL for 4 mg/kg b.i.d. Average exposure to bosentan in paediatric patients was about half the exposure in adult patients at 125 mg b.i.d. maintenance dose but showed large overlap with the findings in adults. Based on the findings in studies BREATHE-3 and FUTURE 1, it appears that the exposure to bosentan reaches a plateau at lower doses in paediatric patients than in adults, and that doses higher than 2 mg/kg b.i.d. will not result in greater exposure to bosentan in paediatric patients.

The consequences of these findings regarding hepatotoxicity are unknown. Gender and the concomitant use of intravenous epoprostenol had no significant effect on the pharmacokinetics of bosentan.

Hepatic impairment

In patients with mildly impaired liver function (Child-Pugh class A) no relevant changes in the pharmacokinetics have been observed. The steady state AUC of bosentan was 9% higher and the AUC of the active metabolite, Ro 48-5033, was 33% higher 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 Tracleer is contra-indicated in this patient population (see section 4.3).

Renal impairment

In patients with severe renal impairment (creatinine clearance 15–30 ml/min), plasma concentrations of bosentan decreased by approximately 10%. Plasma concentrations of bosentan metabolites increased about 2-fold in these patients as compared to subjects with normal renal function. No dose adjustment is required in patients with renal impairment. There is no specific clinical experience in patients undergoing dialysis. Based on physicochemical properties and the high degree of protein binding, bosentan is not expected to be removed from the circulation by dialysis to any significant extent (see section 4.2).

5.3 Preclinical safety data

A 2-year carcinogenicity study in mice showed an increased combined incidence of hepatocellular adenomas and carcinomas in males, but not in females, at plasma concentrations about 2 to 4 times the plasma concentrations achieved at the therapeutic dose in humans. 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 males, but not in females, at plasma concentrations about 9 to 14 times the plasma concentrations achieved at the therapeutic dose in humans. Bosentan was negative in tests for genotoxicity. There was evidence for a mild thyroid hormonal imbalance induced by bosentan in rats. However, there was no evidence of bosentan affecting thyroid function (thyroxine, TSH) in humans.

The effect of bosentan on mitochondrial function is unknown.

Bosentan has been shown to be teratogenic in rats at plasma levels higher than 1.5 times the plasma concentrations achieved at the therapeutic dose in humans. Teratogenic effects, including malformations of the head and face and of the major vessels, were dose dependent. The similarities of the pattern of malformations observed with other ET receptor antagonists and in ET knock-out mice indicate a class effect. Appropriate precautions must be taken for women of child-bearing potential (see sections 4.3, 4.4, 4.6).

In fertility studies in male and female rats at plasma concentrations 21 and 43 times, respectively, the expected therapeutic level in humans, no effects on sperm count, motility and viability, or on mating performance or fertility were observed, nor was there any adverse effect on the development of the pre-implantation embryo or on implantation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Maize starch
Pregelatinised starch
Sodium starch glycollate
Povidone
Glycerol dibehenate
Magnesium stearate

Film coat:

Hypromellose
Glycerol triacetate
Talc
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Ethylcellulose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PE/PVDC/aluminium-blisters containing 14 film-coated tablets.
Cartons contain 56 or 112 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Actelion Registration Ltd
BSI Building 13th Floor
389 Chiswick High Road
London W4 4AL
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/220/004
EU/1/02/220/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 May 2002

Date of renewal: 15 May 2007

10. DATE OF REVISION OF THE TEXT

January 2010

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu/>.

1. NAME OF THE MEDICINAL PRODUCT

Tracleer 32 mg dispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 32 mg bosentan (as monohydrate).
Excipient: 3.7 mg of Aspartame (E951) are present in each dispersible tablet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet:

Pale yellow to off-white, clover-shape tablets, quadrisected on one side and debossed with “32” on the other side. The dispersible tablet can be divided into four equal parts.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:

- Primary (idiopathic and familial) PAH
- PAH secondary to scleroderma without significant interstitial pulmonary disease
- PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger’s physiology

Some improvements have also been shown in patients with PAH WHO functional class II (see section 5.1).

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see section 5.1).

4.2 Posology and method of administration

Tablets are to be taken orally morning and evening, with or without food.

The dispersible tablets should be added to a little water on a spoon, and the liquid stirred to aid dissolution, before swallowing. A little more water should be added to the spoon and swallowed by the patient, to make sure all of the medicine has been administered. If possible, a glass of water should be taken to ensure that all the medicine has been ingested. If necessary the dispersible tablet can be divided by breaking it along the lines cut into the surface (see section 6.6).

The dispersible tablet has been studied only in paediatric patients. Direct bioavailability comparison has not been performed between dispersible tablets and film coated tablets. Thus its use should be reserved for patients who cannot take the film-coated tablet.

Pulmonary arterial hypertension

Treatment should only be initiated and monitored by a physician experienced in the treatment of pulmonary arterial hypertension.

In adult patients, Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

For paediatric patients aged 2 years or older, the optimal maintenance dose has not been defined in well-controlled studies. However, paediatric pharmacokinetic data have shown that bosentan plasma concentrations in children were on average lower than in adult patients and were not increased by increasing the dose of Tracleer above 2 mg/kg twice daily (see section 5.2). Based on these pharmacokinetic results, higher doses are unlikely to be more effective, and greater adverse event rates cannot formally be excluded in young children if the dose is increased. No clinical study has been conducted to compare the efficacy/safety ratio of 2 mg/kg to 4 mg/kg twice daily in children.

There is only limited clinical experience in paediatric patients under 2 years of age

In the case of clinical deterioration (e.g., decrease in 6-minute walk test distance by at least 10% compared with pre-treatment measurement) despite Tracleer treatment for at least 8 weeks (target dose for at least 4 weeks), alternative therapies should be considered. However, some patients who show no response after 8 weeks of treatment with Tracleer may respond favourably after an additional 4 to 8 weeks of treatment.

In the case of late clinical deterioration despite treatment with Tracleer (i.e., after several months of treatment), the treatment should be re-assessed. Some patients not responding well to 125 mg twice daily of Tracleer may slightly improve their exercise capacity when the dose is increased to 250 mg twice daily. A careful risk/benefit assessment should be made, taking into consideration that the liver toxicity is dose dependent (see sections 4.4 and 5.1).

Discontinuation of treatment

There is limited experience with abrupt discontinuation of Tracleer. No evidence for acute rebound has been observed. However, to avoid the possible occurrence of harmful clinical deterioration due to potential rebound effect, gradual dose reduction (halving the dose for 3 to 7 days) should be considered. Intensified monitoring is recommended during the discontinuation period. If the decision to withdraw Tracleer is taken, it should be done gradually while an alternative therapy is introduced.

Systemic sclerosis with ongoing digital ulcer disease

Treatment should only be initiated and monitored by a physician experienced in the treatment of systemic sclerosis.

Tracleer treatment should be initiated at a dose of 62.5 mg twice daily for 4 weeks and then increased to the maintenance dose of 125 mg twice daily.

Controlled clinical study experience in this indication is limited to 6 months (see section 5.1).

The patient's response to treatment and need for continued therapy should be re-evaluated on a regular basis. A careful risk/benefit assessment should be made, taking into consideration the liver toxicity of bosentan (see sections 4.4 and 4.8).

There are no data on the safety and efficacy in patients under the age of 18 years. Kinetic data are not available for Tracleer in young children with this disease.

Special populations

Dosage in hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment (i.e., Child-Pugh class A) (see section 5.2). Tracleer is contraindicated in patients with moderate to severe liver dysfunction (see sections 4.3, 4.4 and 5.2).

Dosage in renal impairment

No dose adjustment is required in patients with renal impairment. No dose adjustment is required in patients undergoing dialysis (see section 5.2).

Dosage in elderly patients

No dose adjustment is required in patients over the age of 65 years.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Moderate to severe hepatic impairment, i.e. Child-Pugh Class B or C (see section 5.2)
- Baseline values of liver aminotransferases, i.e., aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT), greater than 3 times the upper limit of normal (see section 4.4)
- Concomitant use of cyclosporine A (see section 4.5)
- Pregnancy (see section 4.4 and 4.6)
- Women of childbearing potential who are not using reliable methods of contraception (see sections 4.4, 4.5 and 4.6)

4.4 Special warnings and precautions for use

The efficacy of Tracleer has not been established in patients with severe pulmonary arterial hypertension. Transfer to a therapy that is recommended at the severe stage of the disease (e.g., epoprostenol) should be considered if the clinical condition deteriorates (see section 4.2).

The benefit/risk balance of bosentan has not been established in patients with WHO class I functional status of pulmonary arterial hypertension.

Tracleer should only be initiated if the systemic systolic blood pressure is higher than 85 mmHg.

Tracleer has not been shown to have a beneficial effect on the healing of existing digital ulcers.

Liver function

Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment but may also occur late in treatment (see section 4.8). These increases may be partly due to competitive inhibition of the elimination of bile salts from hepatocytes but other mechanisms, which have not been clearly established, are probably also involved in the occurrence of liver dysfunction. The accumulation of bosentan in hepatocytes leading to cytolysis with potentially severe damage of the liver, or an immunological mechanism, are not excluded. Liver dysfunction risk may also be increased when medicinal products that are inhibitors of the bile salt export pump (BSEP), e.g., rifampicin, glibenclamide and cyclosporine A (see sections 4.3 and 4.5), are co-administered with bosentan, but limited data are available.

Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Tracleer. In addition, liver aminotransferase levels must be measured 2 weeks after any dose increase.

Recommendations in case of ALT/AST elevations

ALT/AST levels	Treatment and monitoring recommendations
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> 3 and ≤ 5 × ULN	Confirm by another liver test; if confirmed, reduce the daily dose or stop treatment (see section 4.2), monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider continuing or re-introducing Tracleer according to the conditions described below.
> 5 and ≤ 8 × ULN	Confirm by another liver test; if confirmed, stop treatment and monitor aminotransferase levels at least every 2 weeks. If the aminotransferase levels return to pre-treatment values consider re-introducing Tracleer according to the conditions described below.
> 8 × ULN	Treatment must be stopped and re-introduction of Tracleer is not to be considered.

In case of associated clinical symptoms of liver injury, i.e., nausea, vomiting, fever, abdominal pain, jaundice, unusual lethargy or fatigue, flu-like syndrome (arthralgia, myalgia, fever), treatment must be stopped and re-introduction of Tracleer is not to be considered.

Re-introduction of treatment

Re-introduction of treatment with Tracleer should only be considered if the potential benefits of treatment with Tracleer outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. Re-introduction must follow the guidelines detailed in section 4.2. **Aminotransferase levels must then be checked within 3 days after re-introduction, then again after a further 2 weeks, and thereafter according to the recommendations above.**

ULN= Upper Limit of Normal

Haemoglobin concentration

Treatment with bosentan has been associated with dose-related decreases in haemoglobin concentration (see section 4.8). In placebo-controlled studies, bosentan-related decreases in haemoglobin concentration were not progressive, and stabilised after the first 4–12 weeks of treatment. It is recommended that haemoglobin concentrations be checked prior to initiation of treatment, every month during the first 4 months, and quarterly thereafter. If a clinically relevant decrease in haemoglobin concentration occurs, further evaluation and investigation should be undertaken to determine the cause and need for specific treatment. In the post-marketing period, cases of anaemia requiring red blood cell transfusion have been reported (see section 4.8).

Women of child-bearing potential

Tracleer treatment must not be initiated in women of child-bearing potential unless they practice reliable contraception (see section 4.5) and the result of the pre-treatment pregnancy test is negative (see section 4.6).

Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods 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 section 4.5). Therefore, women of child-bearing 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 gynaecologist 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.

Pulmonary veno-occlusive disease

Cases of pulmonary oedema have been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive disease. Consequently, should signs of pulmonary oedema 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 oedema in patients treated with Tracleer who had a suspected diagnosis of pulmonary veno-occlusive disease.

Pulmonary arterial hypertension patients with concomitant left ventricular failure

No specific study has been performed in patients with pulmonary hypertension and concomitant left ventricular dysfunction. However, 1,611 patients (804 Tracleer- and 807 placebo-treated patients) with severe chronic heart failure (CHF) were treated for a mean duration of 1.5 years in a placebo-controlled study (study AC-052-301/302 [ENABLE 1 & 2]). In this study there was an increased incidence of hospitalisation due to CHF during the first 4 - 8 weeks of treatment with Tracleer, which could have been the result of fluid retention. In this study, fluid retention was manifested by early weight gain, decreased haemoglobin concentration and increased incidence of leg oedema. At the end of this study, there was no difference in overall hospitalisations for heart failure nor in mortality between Tracleer- and placebo-treated patients. Consequently, it is recommended that patients be monitored for signs of fluid retention (e.g., weight gain), especially if they concomitantly suffer from severe systolic dysfunction. Should this occur, starting treatment with diuretics is recommended, or the dose of existing diuretics should be increased. Treatment with diuretics should be considered in patients with evidence of fluid retention before the start of treatment with Tracleer.

Pulmonary arterial hypertension associated with HIV infection

There is limited clinical study experience with the use of Tracleer in patients with PAH associated with HIV infection, treated with antiretroviral medicinal products (see section 5.1). An interaction study between bosentan and lopinavir+ritonavir in healthy subjects showed increased plasma concentrations of bosentan with the maximum level during the first 4 days of treatment (see section 4.5). When treatment with Tracleer is initiated in patients who require ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be closely monitored with special attention, at the beginning of the initiation phase, to the risk of hypotension and to liver function tests. An increased long-term risk of hepatic toxicity and haematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. Due to the potential for interactions related to the inducing effect of bosentan on CYP450 (see section 4.5), which could affect the efficacy of antiretroviral therapy, these patients should also be monitored carefully regarding their HIV infection.

Concomitant use with other medicinal products

Glibenclamide: Tracleer should not be used concomitantly with glibenclamide, due to an increased risk of elevated liver aminotransferases (see section 4.5). An alternative antidiabetic medicinal product should be used in patients in whom an antidiabetic treatment is indicated.

Fluconazole: concomitant use of Tracleer with fluconazole is not recommended (see section 4.5). Although not studied, this combination may lead to large increases in plasma concentrations of bosentan.

Rifampicin: co-administration of Tracleer with rifampicin is not recommended (see section 4.5).

Concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor should be avoided (see section 4.5).

Tracleer 32 mg dispersible tablets contain a source of phenylalanine (Aspartame – E951). This may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

Bosentan is an inducer of the cytochrome P450 (CYP) isoenzymes CYP2C9 and CYP3A4. *In vitro* data also suggest an induction of CYP2C19. Consequently, plasma concentrations of substances metabolised by these isoenzymes will be decreased when Tracleer is co-administered. The possibility of altered efficacy of medicinal products metabolised 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 is metabolised by CYP2C9 and CYP3A4. Inhibition of these isoenzymes may increase the plasma concentration of bosentan (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been studied. The combination should be used with caution. Concomitant administration with fluconazole, which inhibits mainly CYP2C9, but to some extent also CYP3A4, could lead to large increases in plasma concentrations of bosentan. The combination is not recommended. For the same reason, concomitant administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole and ritonavir) and a CYP2C9 inhibitor (such as voriconazole) with Tracleer is not recommended.

Specific interaction studies have demonstrated the following:

Cyclosporine A: co-administration of Tracleer and cyclosporine A (a calcineurin inhibitor) is contraindicated (see section 4.3). Indeed, when co-administered, initial trough concentrations of bosentan were approximately 30-fold higher than those measured after bosentan alone. At steady state, bosentan plasma concentrations were 3- to 4-fold higher than with bosentan alone. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. The blood concentrations of cyclosporine A (a CYP3A4 substrate) decreased by approximately 50%. This is most likely due to induction of CYP3A4 by bosentan.

Tacrolimus, sirolimus: co-administration of tacrolimus or sirolimus and Tracleer has not been studied in man but co-administration of tacrolimus or sirolimus and Tracleer may result in increased plasma concentrations of bosentan in analogy to co-administration with cyclosporine A. Concomitant Tracleer may reduce the plasma concentrations of tacrolimus and sirolimus. Therefore, concomitant use of Tracleer and tacrolimus or sirolimus is not advisable. Patients in need of the combination should be closely monitored for adverse events related to Tracleer and for tacrolimus and sirolimus blood concentrations.

Glibenclamide: co-administration of Tracleer 125 mg twice daily for 5 days decreased the plasma concentrations of glibenclamide (a CYP3A4 substrate) by 40%, with potential significant decrease of the hypoglycaemic effect. The plasma concentrations of bosentan were also decreased by 29%. In addition, an increased incidence of elevated aminotransferases was observed in patients receiving concomitant therapy. Both glibenclamide and bosentan inhibit the bile salt export pump, which could explain the elevated aminotransferases. In this context, this combination should not be used (see section 4.4). No drug-drug interaction data are available with the other sulfonylureas.

Hormonal contraceptives: Co-administration of Tracleer 125 mg twice daily for 7 days with a single dose of oral contraceptive containing norethisterone 1 mg + ethinyl estradiol 35 mcg decreased the AUC of norethisterone and ethinyl estradiol by 14% and 31%, respectively. However, decreases in exposure were as much as 56% and 66%, respectively, in individual subjects. Therefore, 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 sections 4.4, 4.6).

Warfarin: co-administration of bosentan 500 mg twice daily for 6 days decreased the plasma concentrations of both S-warfarin (a CYP2C9 substrate) and R-warfarin (a CYP3A4 substrate) by 29% and 38%, respectively. Clinical experience of concomitant administration of bosentan with warfarin in patients with pulmonary arterial hypertension did not result in clinically relevant changes in International Normalized Ratio (INR) or warfarin dose (baseline versus end of the clinical studies).

In addition, the frequency of changes in warfarin dose during the studies due to changes in INR or due to adverse events was similar among bosentan- and placebo-treated patients. No dose adjustment is needed for warfarin and similar oral anticoagulant agents when bosentan is initiated but intensified monitoring of INR is recommended, especially during bosentan initiation and the up-titration period.

Simvastatin: co-administration of Tracleer 125 mg twice daily for 5 days decreased the plasma concentrations of simvastatin (a CYP3A4 substrate), and its active β -hydroxy acid metabolite by 34% and 46%, respectively. The plasma concentrations of bosentan were not affected by concomitant simvastatin. Monitoring of cholesterol levels and subsequent dosage adjustment should be considered.

Ketoconazole: co-administration of Tracleer 62.5 mg twice daily for 6 days and ketoconazole, a potent CYP3A4 inhibitor, increased the plasma concentrations of bosentan approximately 2-fold. No dose adjustment of Tracleer is considered necessary. Although not demonstrated through *in vivo* studies, similar increases in bosentan plasma concentrations are expected with the other potent CYP3A4 inhibitors (such as itraconazole and ritonavir). However, when combined with a CYP3A4 inhibitor, patients who are poor metabolisers of CYP2C9 are at risk of increases in bosentan plasma concentrations that may be of higher magnitude, thus leading to potential harmful adverse events.

Rifampicin: co-administration in 9 healthy subjects of Tracleer 125 mg twice daily for 7 days and rifampicin, a potent inducer of CYP2C9 and CYP3A4, decreased the plasma concentrations of bosentan by 58%, and this decrease could achieve almost 90% in an individual case. A subsequent significantly reduced effect of bosentan is expected when it is co-administered with rifampicin. Data on other CYP3A4 inducers, e.g. carbamazepine, phenobarbital, phenytoin and St. John's wort are lacking, but their concomitant administration is expected to lead to reduced systemic exposure to bosentan. A clinically significant reduction of efficacy cannot be excluded.

Epoprostenol: limited data obtained from a study (AC-052-356, BREATHE-3) in which 10 paediatric patients received the combination of Tracleer and epoprostenol indicate 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 section 5.1).

Sildenafil: co-administration of Tracleer 125 mg twice daily (steady state) with sildenafil 80 mg three times a day (at steady state) concomitantly administered during 6 days in healthy volunteers resulted in a 63% decrease of the sildenafil AUC and a 50% increase of the bosentan AUC. Caution is recommended in case of co-administration.

Digoxin: co-administration of bosentan 500 mg twice daily for 7 days decreased the AUC, C_{max} and C_{min} of digoxin by 12%, 9% and 23%, respectively. The mechanism for this interaction may be induction of P-glycoprotein. This interaction is unlikely to be of clinical relevance.

Antiretroviral agents :

Lopinavir+Ritonavir (and other boosted protease inhibitors): Co-administration of Tracleer 125 mg twice daily and lopinavir+ritonavir 400+100mg twice daily during 9.5 days in healthy volunteers, resulted in initial trough plasma concentrations of bosentan that were approximately 48-fold higher than those measured after Tracleer administered alone. On day 9, plasma concentrations of bosentan were approximately 5-fold higher 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. When administered concomitantly with lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer should be monitored.

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. Appropriate monitoring of the HIV therapy is recommended. Similar effects would be expected with other ritonavir-boosted protease inhibitors (see section 4.4.).

Other antiretroviral agents:

No specific recommendation can be made with regard to other available antiretroviral agents due to the lack of data. It is emphasized that due to a marked hepatotoxicity of nevirapine that could cumulate with bosentan liver toxicity, this combination is not recommended.

4.6 Pregnancy and lactation

Pregnancy

Studies in animals have shown reproductive toxicity (teratogenicity, embryotoxicity, see section 5.3). There are no reliable data on the use of Tracleer in pregnant women. The potential risk for humans is still unknown. Tracleer is contraindicated in pregnancy (see section 4.3).

Use in women of child-bearing potential

Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods 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 section 4.5). Therefore, women of childbearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but must 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 gynaecologist 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.

Use during lactation

It is not known whether bosentan is excreted into human breast milk. Breast-feeding is not recommended during treatment with Tracleer.

4.7 Effects on ability to drive and use machines

No studies on the effect of Tracleer on the ability to drive and use machines have been performed. Tracleer may cause dizziness, which could influence the ability to drive or use machines.

4.8 Undesirable effects

Adverse reactions

Integrated findings from placebo-controlled studies

In eight placebo-controlled studies, six of which were for indications other than pulmonary arterial hypertension, a total of 677 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The foreseen duration of treatment ranged from 2 weeks to 6 months. The adverse drug reactions that occurred more frequently on bosentan than on placebo ($\geq 3\%$ of bosentan-treated patients, with $\geq 2\%$ difference) were headache (15.8% vs 12.8%), flushing (6.6% vs 1.7%), abnormal hepatic function (5.9% vs 2.1%), leg oedema (4.7% vs 1.4%), and anaemia (3.4% vs 1.0%), all of which were dose related.

Adverse reactions/undesirable effects are ranked according to frequency using the following convention : Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Frequency categories do not account for other factors, including varying study duration, pre-existing conditions, and baseline patient characteristics. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Placebo-controlled studies in primary (idiopathic/familial) PAH and PAH associated with connective tissue diseases

The table below shows the adverse drug reactions, defined as adverse events reported in $\geq 3\%$ of patients and more frequently on bosentan (125 and 250 mg twice daily) in three placebo-controlled trials (bosentan n = 258, placebo n = 172) in PAH.

System organ class	Frequency	Adverse reaction
Infections and infestations	Common	Upper respiratory tract infection, Nasopharyngitis, Respiratory tract infection, Sinusitis
Blood and lymphatic system disorders	Common	Anaemia
Nervous system disorders	Very common Common	Headache ¹ Syncope
Cardiac disorders	Common	Palpitations
Vascular disorders	Common	Hypotension, Flushing
Hepatobiliary disorders	Very common	Liver function test abnormal
Musculoskeletal and connective tissue disorder	Common	Arthralgia
General disorders and administration site conditions	Very common Common	Oedema ² , Fluid retention Chest pain

¹ Headache was reported in 15.1% of patients on bosentan and 14.5% of patients on placebo.

² Oedema or fluid retention was reported in 11.6% of patients on bosentan and 9.9% of patients on placebo.

Treatment discontinuations due to adverse events, during the clinical studies in patients with pulmonary arterial hypertension, at doses of 125 and 250 mg twice daily, occurred with the same frequency (5.8%) in bosentan and placebo-treated patients.

Placebo-controlled study in PAH associated with congenital heart disease (BREATHE-5)

The safety profile of Tracleer in this population was similar to that observed in the pivotal studies in patients with PAH. Adverse events that occurred in a greater proportion of patients on Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily (n = 37) than on placebo (n = 17) included peripheral oedema (18.9% vs. 5.9%), headache (13.5% vs. 11.8%), palpitations (10.8% vs. 0%), dizziness (8.1% vs. 5.9%) and chest pain (8.1% vs. 0%). Four patients discontinued due to adverse events, two (5.4%) in the bosentan group and two (11.8%) in the placebo group.

Uncontrolled study in patients with PAH associated with HIV infection (BREATHE-4)

The safety profile in this population (n = 16) when treated with Tracleer 62.5 mg twice daily for four weeks, followed by 125 mg twice daily was similar to that observed in the pivotal studies in patients with PAH. The most frequent adverse events were peripheral oedema (31%), headache (19%), abnormal liver function (13%), muscle cramps (13%), fluid retention (13%) and vomiting (13%). Haematological abnormalities (anaemia and decrease in neutrophil count) were observed in some patients (see section 4.4).

Uncontrolled trials in paediatric patients (BREATHE-3; FUTURE 1)

The safety profile in this population (BREATHE-3: n = 19, Tracleer 2 mg/kg twice daily; treatment duration 12 weeks; FUTURE 1: n = 36, Tracleer 2 mg/kg twice daily for 4 weeks followed by 4 mg/kg twice daily; treatment duration 12 weeks) was similar to that observed in the pivotal trials in adult

patients with PAH. In BREATHE-3, the most frequent adverse events were flushing (21%), headache, and abnormal hepatic function (each 16%). In FUTURE-1, the most frequent adverse events were infections (33%) and abdominal pain/discomfort (19%). There were no cases of liver enzyme elevations in the FUTURE-1 study.

Placebo-controlled studies in digital ulcers

The table below shows the adverse drug reactions, defined as adverse events reported in $\geq 3\%$ of patients and more frequently on bosentan (125 mg twice daily) in the two pivotal placebo-controlled studies in digital ulcers (bosentan n = 175, placebo n = 133).

System organ Class	Frequency	Adverse reaction
Infections and infestations	Common	Infected skin ulcer, Urinary tract infection
Blood and lymphatic system disorders	Common	Anaemia, Haemoglobin decrease
Vascular disorders	Common	Flushing
Gastrointestinal disorders	Common	Gastrooesophageal reflux disease, Diarrhoea, Abdominal pain, Constipation
Hepatobiliary disorders	Very common	Liver function test abnormal
Skin and subcutaneous tissue disorders	Common	Erythema
Musculoskeletal and connective tissue disorder	Common	Pain in extremity, Back pain
General disorders and administration site conditions	Very common	Oedema, Fluid retention

Laboratory abnormalities

Liver test abnormalities

Bosentan has been associated with dose-related elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases. In the clinical programme, liver enzyme changes generally occurred within the first 26 weeks of treatment, usually developed gradually, and were mainly asymptomatic. They returned, in all cases during the clinical programme, to pre-treatment levels, without sequelae, within a few days to 9 weeks either spontaneously or after dose reduction or discontinuation. In the post-marketing period rare cases of liver cirrhosis and liver failure have been reported (see end of section 4.8).

The mechanism of this adverse effect is unclear. These elevations in aminotransferases may reverse spontaneously while continuing treatment with the maintenance dose of Tracleer or after dose reduction, but interruption or cessation may be necessary (see section 4.4).

In the eight integrated placebo-controlled studies, six of which were for indications other than pulmonary arterial hypertension, elevations in liver aminotransferases by greater than 3 times the upper limit of normal (ULN) were observed in 11.2% of the bosentan-treated patients as compared to 1.8% of the placebo-treated patients. Bilirubin increases to $> 3 \times$ ULN were associated with aminotransferase increases ($> 3 \times$ ULN) in 2 of 658 (0.3%) of patients treated with bosentan. Nine of the 74 bosentan-treated patients who had elevated liver aminotransferases ($> 3 \times$ ULN) also had symptoms such as abdominal pain, nausea/vomiting, and fever.

In studies in patients with pulmonary arterial hypertension, the incidence of elevated liver aminotransferases ($> 3 \times$ ULN) was 12.8% in bosentan-treated patients (N = 257), 12.3% in patients treated with 125 mg twice daily and 14.3% in patients treated with 250 mg twice daily. Eight-fold

increases were seen in 3.7% of pulmonary arterial hypertension patients on 125 mg twice daily and 7.1% of pulmonary arterial hypertension patients on 250 mg twice daily.

In the two studies in patients with digital ulcers the incidence of elevated liver aminotransferases ($> 3 \times \text{ULN}$) was 11.3% in bosentan-treated patients (N = 168) compared with 0.8% in placebo-treated patients (N = 129). Elevations to $> 8 \times \text{ULN}$ were seen in 2.4% of bosentan-treated patients with digital ulcers.

Haemoglobin

The mean decrease in haemoglobin concentration from baseline to study completion for the bosentan-treated patients was 0.9 g/dl and for the placebo-treated patients was 0.1 g/dl.

In eight placebo-controlled studies, clinically relevant decreases in haemoglobin ($> 15\%$ decrease from baseline resulting in values $< 11 \text{ g/dl}$) were observed in 5.6% of bosentan-treated patients as compared with 2.6% of placebo-treated patients. In patients with pulmonary arterial hypertension treated with doses of 125 and 250 mg twice daily, clinically relevant decreases in haemoglobin occurred in 3.0% and 1.3% of the bosentan- and placebo-treated patients, respectively.

In the two studies in patients with digital ulcers, clinically relevant decreases in haemoglobin (decrease from baseline resulting in haemoglobin values $< 10 \text{ g/dL}$) were observed in 4.2% of bosentan-treated patients (N = 167), compared with 3.1% of placebo-treated patients (N = 129).

In the post-marketing period cases of anaemia requiring red blood cell transfusion have been reported (see end of section 4.8).

Postmarketing experience

The majority of adverse events reported during the post-marketing period have been similar to those reported in clinical studies.

Undesirable effects are ranked under headings of frequency using the following convention; very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$).

Gastrointestinal disorders:

Common: nausea

Uncommon: vomiting, abdominal pain, diarrhoea

Hepato-biliary disorders:

Uncommon: aminotransferase elevations associated with hepatitis and/or jaundice

Rare: liver cirrhosis, liver failure

Skin and subcutaneous tissue disorders:

Uncommon: hypersensitivity reactions including dermatitis, pruritus and rash

Immune system disorders:

Rare: anaphylaxis and/or angioedema

Blood and lymphatic system disorders:

Common: anaemia or haemoglobin decreases, sometimes requiring red blood cell transfusion (see section 4.4)

Uncommon: thrombocytopenia

Rare: neutropenia, leukopenia

In the post-marketing period rare cases of unexplained hepatic cirrhosis were reported after prolonged therapy with Tracleer in patients with multiple co-morbidities and therapies medicinal products. There have also been rare reports of liver failure. These cases reinforce the importance of strict adherence to the monthly schedule for monitoring of liver function for the duration of treatment with Tracleer (see section 4.4).

4.9 Overdose

Bosentan has been administered as a single dose of up to 2400 mg to healthy subjects and up to 2000 mg/day for 2 months in patients with a disease other than pulmonary hypertension. The most common adverse event was headache of mild to moderate intensity.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antihypertensives, ATC code: C02KX01

Mechanism of action

Bosentan is a dual endothelin receptor antagonist (ERA) with affinity for both endothelin A and B (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-1 (ET-1) is one of the most potent vasoconstrictors known and can also promote fibrosis, cell proliferation, cardiac hypertrophy, and remodeling and is pro-inflammatory. These effects are mediated by endothelin binding to ET_A and ET_B receptors located in the endothelium and vascular smooth muscle cells. ET-1 concentrations in tissues and plasma are increased in several cardiovascular disorders and connective tissue diseases, including pulmonary arterial hypertension, scleroderma, acute and chronic heart failure, myocardial ischaemia, systemic hypertension and atherosclerosis, suggesting a pathogenic role of ET-1 in these diseases. In pulmonary arterial hypertension and heart failure, in the absence of endothelin receptor antagonism, elevated ET-1 concentrations are strongly correlated with the severity and prognosis of these diseases.

Bosentan competes with the binding of ET-1 and other ET peptides to both ET_A and ET_B receptors, with a slightly higher affinity for ET_A receptors ($K_i = 4.1\text{--}43$ nanomolar) than for ET_B receptors ($K_i = 38\text{--}730$ nanomolar). Bosentan specifically antagonises ET receptors and does not bind to other receptors.

Efficacy

Animal models

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 in the lungs.

Efficacy in adult patients with pulmonary arterial hypertension

Two randomised, double-blind, multi-centre, placebo-controlled studies have been conducted in 32 (Study AC-052-351) and 213 (Study AC-052-352, BREATHE-1) adult patients with WHO functional class III–IV pulmonary arterial hypertension (primary pulmonary hypertension or pulmonary hypertension secondary mainly to scleroderma). After 4 weeks of Tracleer 62.5 mg twice daily, the maintenance doses studied in these studies were 125 mg twice daily in AC-052-351 and 125 mg twice daily and 250 mg twice daily in AC-052-352.

Tracleer was added to patients' current therapy, which could include a combination of anticoagulants, vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digoxin, but not epoprostenol. Control was placebo plus current therapy.

The primary endpoint for each study was change in 6-minute walk distance at 12 weeks for the first study and 16 weeks for the second study. In both studies, treatment with Tracleer resulted in significant increases in exercise capacity. The placebo-corrected increases in walk distance compared to baseline were 76 metres ($p = 0.02$; t-test) and 44 metres ($p = 0.0002$; Mann-Whitney U test) at the primary endpoint of each study, respectively. The differences between the two groups 125 mg twice daily and 250 mg twice daily were not statistically significant but there was a trend towards improved exercise capacity in the group treated with 250 mg twice daily.

The improvement in walk distance was apparent after 4 weeks of treatment, was clearly evident after 8 weeks of treatment and was maintained for up to 28 weeks of double-blind treatment in a subset of the patient population.

In a retrospective responder analysis based on change in walking distance, WHO functional class and dyspnoea of the 95 patients randomised to Tracleer 125 mg twice daily in the placebo-controlled studies, it was found that at week 8, 66 patients had improved, 22 were stable and 7 had deteriorated. Of the 22 patients stable at week 8, 6 improved at week 12/16 and 4 deteriorated compared with baseline. Of the 7 patients that deteriorated at week 8, 3 improved at week 12/16 and 4 deteriorated compared with baseline.

Invasive haemodynamic parameters were assessed in the first study only. Treatment with Tracleer led to a significant increase in cardiac index associated with a significant reduction in pulmonary artery pressure, pulmonary vascular resistance and mean right atrial pressure.

A reduction in symptoms of pulmonary arterial hypertension was observed with Tracleer treatment. Dyspnoea measurement during walk tests showed an improvement in Tracleer-treated patients. In the AC-052-352 study, 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%). The overall change in WHO functional class during both studies was significantly better among Tracleer-treated patients as compared with placebo-treated patients. Treatment with Tracleer was associated with a significant reduction in the rate of clinical worsening compared with placebo at 28 weeks (10.7% vs 37.1%, respectively; $p = 0.0015$).

In a randomised, double-blind, multi-centre, placebo-controlled study (AC-052-364; EARLY), 185 PAH patients in WHO functional class II (mean baseline 6-minute walk distance of 435 metres) 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 6 months. Enrolled patients were PAH-treatment-naïve ($n = 156$) or on a stable dose of sildenafil ($n = 29$). The co-primary endpoints were percentage change from baseline in PVR and change from baseline in 6-minute walk distance to Month 6 versus placebo. The table below illustrates the pre-specified protocol analyses.

	PVR (dyn.sec/cm⁵)		6-Minute Walk Distance (m)	
	Placebo (n=88)	Bosentan (n=80)	Placebo (n=91)	Bosentan (n=86)
Baseline (BL); mean (SD)	802 (365)	851 (535)	431 (92)	443 (83)
Change from BL; mean (SD)	128 (465)	-69 (475)	-8 (79)	11 (74)
Treatment effect	-22.6%		19	
95% CL	-34, -10		-4, 42	
P-value	< 0.0001		0.0758	

Treatment with bosentan was associated with a reduction in the rate of clinical worsening, defined as a composite of symptomatic progression, hospitalisation for PAH and death, compared with placebo (proportional risk reduction 77%, 95% CI 20%–94%, $p = 0.0114$). The treatment effect was driven by improvement in the component symptomatic progression. There was one hospitalisation related to PAH worsening in the bosentan group and 3 hospitalisations in the placebo group. Only one death

occurred in each treatment group during the 6-month double-blind study period, therefore no conclusion can be drawn on survival.

In a prospective, multi-centre, randomized, double-blind, placebo-controlled study (BREATHE-5), patients with pulmonary arterial hypertension WHO functional Class III and Eisenmenger physiology associated with congenital heart disease received Tracleer 62.5 mg bid for 4 weeks, then 125 mg b.i.d. for a further 12 weeks (n = 37), or placebo (n = 17). The primary objective was to show that Tracleer did not worsen hypoxaemia. After 16 weeks, the mean oxygen saturation was increased in the bosentan group by 1.0% (95% CI -0.7; 2.8%) as compared to the placebo group, showing that bosentan did not worsen hypoxemia. The mean pulmonary vascular resistance was significantly reduced in the bosentan group (with a predominant effect observed in the subgroup of patients with bidirectional intracardiac shunt). After 16 weeks, the mean placebo-corrected increase in 6-minute walk distance was 53 meters (p = 0.0079) reflecting improvement of exercise capacity.

An open label, non-comparative study (AC-052-362; BREATHE-4) was performed in 16 patients with WHO Class III PAH associated with HIV infection. Patients were treated with Tracleer 62.5 mg bid for 4 weeks followed by 125 mg bid for a further 12 weeks. After 16 weeks treatment, there were significant improvements from baseline in exercise capacity: mean increase in 6-minute walk test: +91.4 meters from 332.6 meters on average at baseline (p < 0.001). No formal conclusion can be drawn regarding the effects of bosentan on antiretroviral drug efficacy (see also Section 4.4).

There are no studies to demonstrate beneficial effects on survival of treatment with Tracleer. However, long-term vital status was recorded for all 235 patients who were treated with bosentan in the two pivotal placebo-controlled studies (AC-052-351 and AC-052-352) and/or their two uncontrolled, open-label extensions. The mean duration of exposure to bosentan was 1.9 years ± 0.7 years; [min: 0.1; max: 3.3 years] and patients were observed for a mean of 2.0 ± 0.6 years. The majority of patients were diagnosed as PPH (72%) and were in WHO functional class III (84%). In this total population, Kaplan-Meier estimates of survival were 93% and 84% after 1 and 2 years after the start of treatment with Tracleer, respectively. Survival estimates were lower in the subgroup of patients with PAH secondary to systemic sclerosis. The estimates may have been influenced by the initiation of epoprostenol treatment in 43/235 patients.

Study performed in children with pulmonary arterial hypertension

One study has been conducted in children with pulmonary hypertension. Tracleer has been evaluated in an open-label non-controlled study in 19 paediatric patients with pulmonary arterial hypertension (AC-052-356, BREATHE-3: primary pulmonary hypertension 10 patients, and pulmonary arterial hypertension related to congenital heart diseases 9 patients). This study was primarily designed as a pharmacokinetic study (see section 5.2). Patients were divided into and dosed according to three body-weight groups (see section 4.2) for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. The age range was 3–15 years. Patients were in WHO functional class II (N = 15 patients, 79%) or class III (N = 4 patients, 21%) at baseline.

Haemodynamics were measured in 17 patients. The mean increase from baseline in cardiac index was 0.5 l/min/m², the mean decrease in mean pulmonary arterial pressure was 8 mmHg, and the mean decrease in pulmonary vascular resistance was 389 dyn·sec·cm⁻⁵. These haemodynamic improvements from baseline were similar with or without co-administration of epoprostenol. Changes in exercise test parameters at week 12 from baseline were highly variable and none were significant.

Combination 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 multi-centre, randomised, double-blind, parallel-group study 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-controlled study; 10 of the 19 paediatric patients were on concomitant Tracleer and epoprostenol therapy during the 12-week study. The safety profile of the combination was not

different from the one expected with each component and the combination therapy was well tolerated in children and adults. The clinical benefit of the combination has not been demonstrated.

Systemic sclerosis with digital ulcer disease

Two randomised, double-blind, multi-centre, placebo-controlled studies have been conducted in 122 (Study AC-052-401, RAPIDS-1) and 190 (Study AC-052-331, RAPIDS-2) adult patients with systemic sclerosis and digital ulcer disease (either ongoing digital ulcers or a history of digital ulcers within the last year). In study AC-052-331, patients had to have at least one digital ulcer of recent onset, and across the two studies 85% of patients had ongoing digital ulcer disease at baseline. After 4 weeks of Tracleer 62.5 mg twice daily, the maintenance doses studied in both these studies were 125 mg twice daily. The duration of double-blind therapy was 16 weeks in study AC-052-401, and 24 weeks in study AC-052-331.

Background treatments for systemic sclerosis and digital ulcers were permitted if they remained constant for at least 1 month prior to the start of treatment and during the double-blind study period.

The number of new digital ulcers from baseline to study endpoint was a primary endpoint in both studies. Treatment with Tracleer resulted in fewer new digital ulcers for the duration of therapy, compared with placebo. In study AC-052-401, during 16 weeks of double-blind therapy, patients in the bosentan group developed a mean of 1.4 new digital ulcers *vs.* 2.7 new digital ulcers in the placebo group ($p = 0.0042$). In study AC-052-331, during 24 weeks of double-blind therapy, the corresponding figures were 1.9 *vs.* 2.7 new digital ulcers, respectively ($p = 0.0351$). In both studies, patients on bosentan were less likely to develop multiple new digital ulcers during the study and took longer to develop each successive new digital ulcer than did those on placebo. The effect of bosentan on reduction of the number of new digital ulcers was more pronounced in patients with multiple digital ulcers.

No effect of bosentan on time to healing of digital ulcers was observed in either study.

5.2 Pharmacokinetic properties

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.

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.

Absorption

In healthy subjects the absolute bioavailability of bosentan is approximately 50% and is not affected by food. The maximum plasma concentrations are attained within 3–5 hours.

Distribution

Bosentan is highly bound (> 98%) to plasma proteins, mainly albumin. Bosentan does not penetrate into erythrocytes.

A volume of distribution (V_{ss}) of about 18 litres was determined after an intravenous dose of 250 mg.

Biotransformation and elimination

After a single intravenous dose of 250 mg, the clearance was 8.2 l/h. The terminal elimination half-life ($t_{1/2}$) is 5.4 hours.

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 metabolising liver enzymes. Steady-state conditions are reached within 3–5 days.

Bosentan is eliminated by biliary excretion following metabolism in the liver by the cytochrome P450 isoenzymes, CYP2C9 and CYP3A4. Less than 3% of an administered oral dose is recovered in urine.

Bosentan forms three metabolites and only one of these is pharmacologically active. This metabolite is mainly excreted unchanged via the bile. In adult patients, the exposure to the active metabolite is greater than in healthy subjects. In patients with evidence of the presence of cholestasis, the exposure to the active metabolite may be increased.

Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19 and the P-glycoprotein. *In vitro*, bosentan inhibits the bile salt export pump in hepatocyte cultures.

In vitro data demonstrated that bosentan had no relevant inhibitory effect on the CYP isoenzymes tested (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4). Consequently, bosentan is not expected to increase the plasma concentrations of medicinal products metabolised by these isoenzymes.

Pharmacokinetics in special populations

Based on the investigated range of each variable, 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. No kinetic data are available in children under 2 years.

Children

The pharmacokinetics of single and multiple oral doses were studied in paediatric patients with pulmonary arterial hypertension who were dosed on the basis of body weight (see sections 5.1 BREATHE-3). 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 paediatric 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 with pulmonary arterial hypertension receiving 125 mg b.i.d. At steady state the systemic exposure in paediatric patients weighing 10–20 kg, 20–40 kg and > 40kg were 43%, 67% and 75%, respectively, of the adult systemic exposure.

In a second pharmacokinetics study (FUTURE 1), 36 paediatric patients aged 2–11 years with PAH were treated at 2 and 4 mg/kg b.i.d. with the dispersible tablet. No dose proportionality was observed. Steady-state bosentan plasma concentrations were similar at oral doses of 2 and 4 mg/kg. The AUC_τ was 3,577 ng·h/mL for 2 mg/kg b.i.d. and 3,371 ng·h/mL for 4 mg/kg b.i.d. Average exposure to bosentan in paediatric patients was about half the exposure in adult patients at 125 mg b.i.d. maintenance dose but showed large overlap with the findings in adults. Based on the findings in studies BREATHE-3 and FUTURE 1, it appears that the exposure to bosentan reaches a plateau at lower doses in paediatric patients than in adults, and that doses higher than 2 mg/kg b.i.d. will not result in greater exposure to bosentan in paediatric patients.

The consequences of these findings regarding hepatotoxicity are unknown. Gender and the concomitant use of intravenous epoprostenol had no significant effect on the pharmacokinetics of bosentan.

Hepatic impairment

In patients with mildly impaired liver function (Child-Pugh class A) no relevant changes in the pharmacokinetics have been observed. The steady state AUC of bosentan was 9% higher and the AUC of the active metabolite, Ro 48-5033, was 33% higher 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 Tracleer is contra-indicated in this patient population (see section 4.3).

Renal impairment

In patients with severe renal impairment (creatinine clearance 15–30 ml/min), plasma concentrations of bosentan decreased by approximately 10%. Plasma concentrations of bosentan metabolites increased about 2-fold in these patients as compared to subjects with normal renal function. No dose adjustment is required in patients with renal impairment. There is no specific clinical experience in patients undergoing dialysis. Based on physicochemical properties and the high degree of protein binding, bosentan is not expected to be removed from the circulation by dialysis to any significant extent (see section 4.2).

5.3 Preclinical safety data

A 2-year carcinogenicity study in mice showed an increased combined incidence of hepatocellular adenomas and carcinomas in males, but not in females, at plasma concentrations about 2 to 4 times the plasma concentrations achieved at the therapeutic dose in humans. 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 males, but not in females, at plasma concentrations about 9 to 14 times the plasma concentrations achieved at the therapeutic dose in humans. Bosentan was negative in tests for genotoxicity. There was evidence for a mild thyroid hormonal imbalance induced by bosentan in rats. However, there was no evidence of bosentan affecting thyroid function (thyroxine, TSH) in humans.

The effect of bosentan on mitochondrial function is unknown.

Bosentan has been shown to be teratogenic in rats at plasma levels higher than 1.5 times the plasma concentrations achieved at the therapeutic dose in humans. Teratogenic effects, including malformations of the head and face and of the major vessels, were dose dependent. The similarities of the pattern of malformations observed with other ET receptor antagonists and in ET knock-out mice indicate a class effect. Appropriate precautions must be taken for women of child-bearing potential (see sections 4.3, 4.4, 4.6).

In fertility studies in male and female rats at plasma concentrations 21 and 43 times, respectively, the expected therapeutic level in humans, no effects on sperm count, motility and viability, or on mating performance or fertility were observed, nor was there any adverse effect on the development of the pre-implantation embryo or on implantation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Calcium hydrogen phosphate anhydrous
Croscarmellose sodium
Silica colloidal anhydrous
Tartaric acid
Tutti frutti flavour
Aspartame (E951)
Acesulfame potassium
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

The remaining parts of a divided dispersible tablet can be stored at room temperature and should be used within 7 days.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

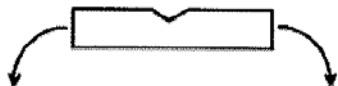
Aluminium /Aluminium peel-push blisters containing 14 dispersible tablets.
Cartons contain 56 dispersible tablets.

6.6 Special precautions for disposal and other handling

The dispersible tablet is contained in a child-proof blister.

Each dispersible tablet can be dissolved in water to make a liquid medicine, by adding the tablet to a little water on a spoon, using enough water to cover the whole tablet. When the tablet has fully dissolved, give the liquid to the patient.

If necessary, the dispersible tablet can be divided by breaking along the lines cut into the surface. Hold the tablet between the thumb and index finger on either side of one of the lines, with the line facing upwards, and break the tablet along the line (see figure below).



The remaining parts of a divided dispersible tablet can be stored at room temperature and should be used within 7 days.

7. MARKETING AUTHORISATION HOLDER

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London W4 4AL
United Kingdom

8. MARKETING AUTHORISATION NUMBERS

EU/1/02/220/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 May 2002

Date of renewal: 15 May 2007

10. DATE OF REVISION OF THE TEXT

January 2010

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.