Summary of Product Characteristics (SmPC)

Tracleer® (bosentan) Abbreviated Prescribing Information (Please refer to the full SmPC before prescribing)
Tracleer 62.5 mg and 125 mg film-coated tablets; 32 mg dispersible tablets

Uses 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 and 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.** Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

Dosage and administration Treatment should only be initiated and monitored by a physician experienced in the treatment of PAH or systemic sclerosis. 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. If necessary the dispersible tablet can be divided along the break-marks. The dispersible tablet has been studied only in paediatric patients with PAH. 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.
In the case of PAH clinical deterioration despite Tracleer treatment for at least 8 weeks, alternative therapies should be considered. However, some PAH patients who show no response after 8 weeks of treatment with Tracleer may respond favourably after an additional 4 to 8 weeks of treatment. PAH 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. If the decision to withdraw Tracleer is taken, it should be done gradually while an alternative therapy is introduced.
Controlled clinical trial experience in patients with digital ulcers associated with systemic sclerosis is limited to 6 months and there are no data on the safety and efficacy in patients under the age of 18 years. The digital ulcer patient's response to treatment and need for continued therapy should be re-evaluated on a regular basis. *Dosage in hepatic impairment* Mild: No dose adjustment required. Moderate/Severe: Contraindicated. *Dosage in renal impairment:* No dose adjustment required. No dose adjustment is required in patients undergoing dialysis. *Dosage in elderly patients:* No dose adjustment required. *Children and patients with low body weight with PAH:* Pediatric pharmacokinetic data have shown that bosentan plasma concentrations in children were not increased by increasing the dose of Tracleer above 2 mg/kg twice daily (see section 5.2). Based on the 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. There is only limited clinical experience in paediatric patients under 2 years of age.

Contraindications Hypersensitivity to the active substance or any of the excipients, moderate to severe hepatic impairment, baseline values of liver aminotransferases (AST and/or ALT), greater than 3 times the upper limit of normal, concomitant use of cyclosporine A, pregnancy, women of childbearing potential who are not using a reliable (barrier)-method of contraception (see later).

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. The benefit/risk balance of Tracleer has not been established in patients with WHO class I functional status of PAH. 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 Tracleer are dose-dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment, but may also occur late in treatment. Recommendations are as follows:

- Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals.
- Liver aminotransferase levels must be measured 2 weeks after any dose increase.
- In the event of a rise in liver aminotransferases treatment should be stopped (>5 and ≤8 x ULN) or dose reduced (>3 and ≤5 x ULN only).
- Re-introduction of treatment should only be considered if the potential treatment benefits outweigh the potential risks and when liver aminotransferase levels are within pre-treatment values. The advice of a hepatologist is recommended. AST/ALT levels must then be checked within 3 days after re-introduction, then again after 2 weeks, and thereafter according to the recommendations above.
- In case of associated clinical symptoms of liver injury, or a >8 x ULN rise in liver aminotransferases, treatment must be stopped and re-introduction of Tracleer is not to be considered.

Haemoglobin concentration Tracleer has been associated with dose-related decreases in haemoglobin concentration. In placebo-controlled studies, decreases 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, monthly for the first 4 months, and quarterly thereafter. In the post-marketing period, cases of anaemia requiring red blood cell transfusion have been reported. *Women of childbearing potential* Not to be initiated in women of childbearing potential unless they practice reliable contraception and have a negative pre-treatment pregnancy test. Before the initiation of Tracleer treatment, the absence of pregnancy should be checked by a negative pregnancy test, appropriate advice on reliable methods of contraception provided, and reliable contraception initiated. Due to potential pharmacokinetic interactions Tracleer may render hormonal contraceptives ineffective. 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. In case of any doubt on the contraceptive advice, 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 are recommended to allow early detection of pregnancy. *Pulmonary veno-occlusive disease (PVOD)* Cases of life threatening pulmonary oedema have been reported with vasodilators (mainly prostacyclin) when used in those patients. Should signs of pulmonary oedema occur in PAH patients, the possibility of associated veno-occlusive disease should be considered. There have been rare reports of pulmonary oedema in patients treated with Tracleer who had a suspected diagnosis of PVOD. *PAH patients with concomitant left ventricular failure* No specific study has been performed. It is recommended that patients be monitored for signs of fluid retention. Should this occur, 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. *PAH associated with HIV infection* (lopinavir+ritonavir *and other boosted protease inhibitors)*) 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 potential for interactions related to the inducing effect of bosentan on CYP450 patients should be monitored carefully regarding their HIV infection and the HIV therapy. Nevirapine: due to a marked hepatotoxicity of nevirapine that could cumulate with bosentan liver toxicity, this combination is not recommended. Other antiretroviral agents: No specific recommendation can be made with regard to other available antiretroviral agents. *Pulmonary hypertension secondary to chronic obstructive pulmonary disease (COPD)* Safety and tolerability of bosentan was investigated in an exploratory, uncontrolled 12-week study in 11 patients with pulmonary hypertension secondary to severe COPD (stage III of GOLD classification). An increase in minute ventilation and a decrease in oxygen saturation were observed and the most frequent adverse event was dyspnoea, which resolved with discontinuation of bosentan. *Concomitant use with other medicinal products Glibenclamide:* Not recommended, due to an increased risk of elevated liver aminotransferases. *Fluconazole:* Not recommended. *Rifampicin:* Not recommended. Concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor should be avoided. *Hormonal contraceptives:* Hormone based contraceptives alone, regardless of the route of administration are not considered as reliable methods of contraception. Tracleer 32 mg dispersible tablets contain a source of phenylalanine (Aspartame – E951). This may be harmful for people with phenylketonuria.

Pregnancy and lactation Tracleer is contraindicated in pregnancy. Tracleer may render hormonal contraceptives ineffective. 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. 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 are recommended to allow early detection of pregnancy. *Use during lactation* Not recommended.

Ability to drive and use machines Tracleer may cause dizziness, which could influence the ability to drive or use machines.

Side effects *Integrated findings from placebo-controlled studies* In eight placebo-controlled studies a total of 677 patients were treated with Tracleer at daily doses ranging from 100 mg to 2000 mg and 288 patients were treated with placebo. The adverse drug reactions that occurred more frequently with Tracleer than with placebo (in ≥3% of Tracleer-treated patients, with ≥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.

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Tracleer BOSENTAN TABLETS

Placebo-controlled studies in primary (idiopathic/familial) PAH and PAH associated with connective tissue disease The table below shows the adverse drug reactions, defined as adverse events reported in ≥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.

Uncontrolled trials in paediatric patients 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, headache, and abnormal hepatic function. In FUTURE-1, the most frequent adverse events were infections and abdominal pain/discomfort. 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 ≥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

Post-marketing experience The majority of adverse events reported during the post-marketing period have been similar to those reported in clinical studies. **Common events** seen included nausea; anaemia or haemoglobin decreases, sometimes requiring red blood cell transfusion; **uncommon events** included vomiting, abdominal pain, diarrhoea, aminotransferase elevations associated with hepatitis and/or jaundice, hypersensitivity reactions including dermatitis, pruritus and rash; thrombocytopenia; **rare events** included liver cirrhosis, liver failure, anaphylaxis and/or angioedema, neutropenia, leukopenia. **Rare cases of unexplained hepatic cirrhosis, reported after prolonged exposure in patients with multiple co-morbidities and therapies with medicinal products, and liver failure have been reported. These cases reinforce the importance of strict adherence to the monthly liver function monitoring during Tracleer treatment.**

Laboratory abnormalities *Liver test abnormalities* In studies in patients with PAH, the incidence of elevated liver aminotransferases (>3 x ULN) was 12.8% in Tracleer-treated patients ($n = 257$), 12.3% in patients treated with 125 mg BD and 14.3% in patients treated with 250 mg BD. Eight-fold increases were seen in 3.7% of PAH patients on 125 mg BD and 7.1% of PAH patients on 250 mg BD. In the two studies in patients with digital ulcers the incidence of elevated liver aminotransferases (>3 x ULN) was 11.3% in bosentan-treated patients ($n = 168$) compared with 0.8% in placebo-treated patients ($n = 129$). Elevations to >8 x ULN were seen in 2.4% of bosentan-treated patients with digital ulcers. *Haemoglobin* The mean decrease in haemoglobin concentration from baseline to trial completion for the Tracleer- and placebo-treated patients was 0.9 g/dl and 0.1 g/dl 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 ($n = 129$).

Overdose Massive overdose may result in pronounced hypotension requiring active cardiovascular support.

Packaging quantity Tracleer 62.5 mg: 14, 56 or 112 film-coated tablets. Tracleer 125 mg: 56 or 112 film-coated tablets. Not all pack sizes may be marketed. Tracleer 32 mg: 56 dispersible tablets

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