Tracleer®

Composition
Active substance: Bosentan (as monohydrate) (62.5 mg or 125 mg).
Excipients: maize starch, pregelatinised maize starch, sodium starch glycollate, povidone, glyceryl behenate, magnesium stearate, hypromellose, glycerol triacetate, talc, titanium dioxide, iron oxide yellow, iron oxide red, ethylcellulose

Pharmaceutical form and weight of active substance per dosage unit
Film-coated tablets
62.5mg (orange white, round, biconvex, with «62.5» stamped on one side) and 125 mg (orange white, oval, biconvex, with «125» stamped on one side)

Indications / Areas of use
Treatment of pulmonary arterial hypertension (PAH) in patients with WHO functional class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Some improvements have also been shown in patients with PAH WHO functional class II.
Reduction in the number of new digital ulcers in patients with systemic sclerosis with active digital ulcer disease.

Posology and method of administration
Treatment should only be initiated and monitored by a doctor with experience in the treatment of pulmonary arterial hypertension and systemic sclerosis. Tracleer® should be taken orally in the morning and evening, with or without food. The film-coated tablets are to be swallowed with water. Patients must be urged to refrain from swallowing the desiccant in the white high density polyethylene bottle.

Pulmonary arterial hypertension (PAH)
Treatment with Tracleer® should be started at a dosage of twice daily 62.5 mg over a period of four weeks, followed by an increase to a maintenance dose of twice daily 125 mg.

Systemic sclerosis with active digital ulcer disease
Treatment with Tracleer® should be started at a dosage of 62.5 mg twice daily over a period of four weeks, followed by an increase to a maintenance dose of 125 mg twice daily. Experience from controlled clinical trials in this indication is limited to a period of 6 months. Response to treatment and the necessity of continuing treatment should be regularly re-evaluated.

Discontinuation of treatment
There has been no adequate experience of sudden discontinuation of Tracleer® treatment. There is no evidence of an acute rebound effect. To avoid possible severe clinical deterioration from any rebound effect, the possibility should be considered of gradually reducing the dose, by halving it for 3 to 7 days. It is recommended that the patient should be closely monitored during the discontinuation.

Dosage of patients with liver disorders
No dose adjustment is necessary for patients with mildly impaired liver function (i.e. Child-Pugh class A) (see section on «Pharmacokinetic properties»). Tracleer® is contraindicated in patients with moderate to severe liver disorders or where liver aminotransferase values are more than three times the upper limit of normal prior to the start of treatment (see sections on «Contraindications», «Special warnings and precautions for use» and «Pharmacokinetic properties»).
See section on «Special warnings and precautions for use» for course of action if liver aminotransferase values rise during treatment

Dosage in patients with kidney disorders
No dose adjustment is needed in patients with impaired renal function or in patients on dialysis (see section on «Pharmacokinetic properties»).

Dosage in older patients
There have been no adequate studies on the affect of age.

Use in children and adolescents
- Pulmonary arterial hypertension
There have been no adequate studies on efficacy and safety in patients aged under 12 years. The following dosage scheme was used in trial AC-052-356 (BREATHE-3):

Body weight (kg)	Initial dose (4 weeks)	Maintenance dose
10 ≤ × ≤20	1× day 31.25 mg	2× day 31.25 mg
20 < × ≤40	2× day 31.25 mg	2× day 62.5 mg
>40 kg	2× day 62.5 mg	2× day 125 mg

* The 31.25 mg dose was obtained from the not divisible 62.5 mg film-coated tablet by using a tablet splitter. There are, however, no data on the content of active substance in the halved tablets. The trial was designed to determine the pharmacokinetics in children. However, the number of patients in each dosage group was too low to establish the optimal dosage regimen for patients aged under 12 years. The pharmacokinetic results showed that the systemic bioavailability was lower than in adults with pulmonary hypertension, which might lead to suboptimal activity on the pulmonary vascular system. There are currently no adequate data on changes in haemodynamics in children. There are no data for children aged under 3 years.

There are only limited data for patients weighing under 40 kg. For dosage for these patients, please refer to the dosage table in the section on «Use in children and adolescents». The 31.25 mg dose was obtained from the unscored 62.5 mg film-coated tablet by using a tablet splitter. There are however no data on the content of active substance in the halved tablets.

- Systemic sclerosis with active digital ulcer disease
There are no data on the safety and efficacy in patients aged under 18 years.

Contraindications
Hypersensitivity to bosentan or to one of the excipients.
Moderate to severe liver disorders (Child-Pugh class B or C see section on Pharmacokinetic properties»).
Raised liver aminotransferases before the start of treatment, i.e. aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) to more than three times the upper normal limit (see section on «Special warnings and precautions for use»).
Pregnancy.
Women of child-bearing age who are not using adequate contraception.
Simultaneous use of cyclosporine A and glibenclamide.

Special warnings and precautions for use
Bosentan's risk-benefit profile has not been investigated in patients with pulmonary hypertension of functional severity corresponding to WHO class I (see section on «Pharmacological properties»).
Treatment with Tracleer® may only be started if the systemic systolic blood pressure is greater than 85 mmHg.
Treatment with Tracleer® had no effect on the healing of existing digital ulcers.

Liver function
The increases in liver aminotransferases (aspartate and/or alanine aminotransferases; AST and/or ALT) associated with bosentan are dose-dependent.
The changes in liver enzyme values typically occur within the first 26 weeks of treatment (see section on «Undesirable effects»), although they may also occur later.
The increases in liver enzyme values generally develop slowly and are asymptomatic. These increases in aminotransferases may drop off spontaneously with continuation of treatment with the maintenance dose for Tracleer® or after a reduction in the dosage. However, interruption or discontinuation of treatment may be required. Rare cases of cirrhosis of the liver and liver failure were reported after release of the drug on to the market. The mechanism of this undesirable effect is unclear.
The rise in aminotransferase values may be linked in part to competitive inhibition of the elimination of bile salts from hepatocytes. However, other mechanisms, which have not yet been clearly proven, are also probably involved in the development of disturbances in liver function. Possibilities which have not been excluded are cytolysis from accumulation of bosentan in hepatocytes - perhaps leading to severe liver damage - or an immunological mechanism. The risk of disturbances to liver function may also be increased if bosentan is administered at the same time as drugs which inhibit the bile salt export pump (BSEP), such as rifampicin, glibenclamide and cyclosporine A (see sections on «Contraindications» and «Interaction with other medicinal products and other forms of interactions»). However, the available data are limited.
The liver aminotransferase values must be measured before the start of treatment and then monthly throughout the treatment with Tracleer®. In addition, liver transaminase values must be measured 2 weeks after every increase in dose.

Recommendations after an increase in the ALT/AST values

Recommendations for treatment and control
ALT/AST >3 and ≤5 × UNV (upper normal value): check by repeating the test. If the finding is confirmed, the daily dose should be reduced or drug treatment discontinued and the aminotransferase values should be checked at least every 2 weeks. Once the aminotransferase values have returned to the levels before the start of treatment, restarting or continuing treatment with Tracleer® may be considered in accordance with the conditions listed below.
ALT/AST >5 and ≤8 × UNV: check by repeating the test. If the finding is confirmed, the drug should be discontinued and the aminotransferase values should be checked at least every 2 weeks. Once the aminotransferase values have returned to the levels before the start of treatment, restarting treatment with Tracleer® may be considered in accordance with the conditions listed below.
ALT/AST >8 × UNV: the drug must be discontinued. Treatment may not be resumed.
If there are clinical symptoms associated with liver damage, i.e. nausea, vomiting, fever, gastric pain, jaundice, unusual lethargy or exhaustion, flu-like symptoms (arthralgia, myalgia, fever), **treatment must be discontinued.**
Resumption of treatment with Tracleer® should not be considered.

Resumption of treatment
Resumption/continuation of treatment should only be considered if the possible benefits of treatment with Tracleer® outweigh the possible risks and if the liver transaminase values have returned to those at the start of treatment. It is recommended to consult a hepatologist. If treatment is resumed, the dosage schedule in the section «Posology and method of administration» should be complied with. **After resumption of treatment, the aminotransferase values must be controlled within the first 3 days, then after a further 2 weeks and then as recommended above.**

Haemoglobin, blood coagulation
Treatment with bosentan has been linked to a dose-dependent decrease in haemoglobin (see section on «Undesirable effects»). The decrease in haemoglobin concentration is not progressive and stabilises within the first 4 to 12 weeks after the start of treatment in placebo-controlled studies. Cases of anaemia that required an erythrocyte transfusion were reported in the post-marketing period (see section on «Undesirable effects»). It is recommended to check the haemoglobin concentration before the start of treatment, at monthly intervals during the first 4 months of treatment and then every 3 months. If there is a clinically relevant reduction in haemoglobin concentration, subsequent evaluations and tests must clarify the cause and the necessity of specific treatment. It is pointed out that for patients treated with oral anticoagulants close monitoring of the International Normalized Ratio (INR) is recommended, particularly at the start of treatment and when the dose is titrated up (see section on «Interaction with other medicinal products and other forms of interactions, warfarin»).

Sickle cell anaemia
There have been isolated post-marketing reports of sickle cell anaemia crises in patients treated with Tracleer® who already had sickle cell anaemia before the start of treatment.

Use in patients with pulmonary veno-occlusive disease (PVOD)
There have been reports of cases of pulmonary oedema after treatment with vasodilators (mainly prostacyclins) of patients with pulmonary veno-occlusive disease (PVOD). For this reason, if symptoms of pulmonary oedema develop in patients with pulmonary arterial hypertension (PAH) after treatment with Tracleer®, the possibility of associated veno-occlusive disease should be considered. There have been isolated post-marketing reports of pulmonary oedema in patients with suspected pulmonary veno-occlusive disease treated with Tracleer®.

Use in patients with pulmonary arterial hypertension accompanied by left heart failure
In the placebo-controlled trials in patients with pulmonary arterial hypertension, peripheral oedema and decreases in haemoglobin values have been reported, without a demonstrable increase in the incidence of early admissions to hospital because of deterioration in the clinical condition. In one trial with patients with severe chronic heart failure, there was an increase in the rate of admissions to hospital because of fluid retention shortly after the start of therapy. As PAH patients can also suffer from concomitant left heart failure and fluid retention was also observed in PAH patients in placebo-controlled trials with Tracleer®, it is recommended to monitor patients for signs of fluid retention (e.g. weight increase). In these cases, it is recommended to start diuretic treatment or to increase the current dose of diuretic. Patients with signs of fluid retention should be treated with diuretics before starting treatment with bosentan.

Pulmonary arterial hypertension in patients with an HIV infection
There is limited experience in the use of Tracleer® in patients with PAH and an HIV infection who are being treated with antiretroviral drugs. An interaction study between bosentan and lopinavir+ritonavir in healthy subjects showed increased plasma concentrations of bosentan, see section on «Interactions »
When treatment with Tracleer® is initiated in patients who require ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer® should be closely monitored. An increased long-term risk of hepatic toxicity and hematological adverse events cannot be excluded when bosentan is used in combination with antiretroviral medicinal products. As there is the possibility of interactions which could influence the efficacy of antiretroviral drugs, the patient's HIV infection should be carefully monitored.

Epoprostenol
The combination of Tracleer® and epoprostenol has been investigated in two trials: BREATHE-2 and BREATHE-3
BREATHE-2 was a multicentre, randomised double blind trial with Tracleer® (n=22) vs. placebo (n=11), on 33 patients with severe pulmonary arterial hypertension, who were simultaneously given epoprostenol.
BREATHE-3 was an open-label, uncontrolled trial. 10 of the 19 paediatric patients were given the combination of Tracleer® and epoprostenol over 12 weeks.
The safety profile did not differ from the safety profile for the individual substances and the combination therapy was well tolerated by both children and adults.
In the study on adults, two patients under Tracleer®/epoprostenol died of progressive disease. The clinical efficacy of the combination could not be demonstrated.

Use in women of child-bearing age
See section on "Pregnancy and lactation"

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.

Simultaneous use of other drugs
See section on «Interactions »

Interactions
Bosentan is an inducer of the cytochrome P450 isoenzymes CYP2C9 and CYP3A4. *In vitro* data indicate that CYP2C19 is also induced. As a consequence, the plasma concentrations of drugs metabolised by these isoenzymes may be reduced with simultaneous administration of Tracleer®. The possibility should be considered that the efficacy of drugs metabolised by these isoenzymes might be altered. The doses of these drugs may have to be adjusted after the start or discontinuation of treatment with Tracleer®, or after a dose change.
Bosentan is metabolised by CYP2C9 and CYP3A4. If these isoenzymes are inhibited, the plasma concentration of bosentan may be raised (see ketoconazole). The influence of CYP2C9 inhibitors on bosentan concentration has not been investigated. Caution is necessary with a combination of this type. Fluconazole predominantly inhibits CYP2C9, but also CYP3A4 to some extent; this might markedly increase the plasma concentrations of bosentan. This combination is not recommended. The simultaneous administration of both a potent CYP3A4 inhibitor (such as ketoconazole, itraconazole or ritonavir) and a CYP2C9 inhibitor (such as voriconazole) together with Tracleer® is not recommended.
Specific investigations on interactions with drugs have given the following results:

Hormonal contraceptives: simultaneous administration of Tracleer® 125 mg 2x daily for 7 days and an oral contraceptive (containing norethisterone 1 mg and ethinyloestradiol 35 µg) reduced the AUC of norethisterone by 14% and that of ethinyloestradiol by 31%. However, reductions of up to 56% or 66%, respectively, were found for individual female volunteers. For this reason, hormonal contraceptives alone, independent of how they are administered (i.e., oral, intramuscular, transdermal, vaginal and implantable forms) are not viewed as reliable contraceptive methods.

Cyclosporine A: simultaneous administration of Tracleer® und cyclosporine A is contraindicated (see section on «Contraindications»). After bosentan 500 mg twice daily was co-administered with cyclosporine A, the initial trough concentrations of bosentan were about 30-fold higher than with bosentan alone. At steady state, bosentan plasma concentrations were 3- to 4-fold higher than after administration of bosentan alone. The mechanism of this interaction is most likely inhibition of transport protein-mediated uptake of bosentan into hepatocytes by cyclosporine. The

plasma concentrations of cyclosporine A (a CYP3A4 substrate) decreased by about 50%. Both cyclosporine and bosentan inhibit the bile salt export pump, which can lead to raised aminotransferase values.

Tacrolimus, Sirolimus: simultaneous administration of tacrolimus or sirolimus and Tracleer® in man has not been investigated. In analogy to the simultaneous administration of cyclosporine A, simultaneous administration of tacrolimus or sirolimus may lead to increased plasma concentrations of bosentan. Simultaneous administration of Tracleer® may decrease the plasma concentrations of tacrolimus or sirolimus. For this reason, simultaneous administration of Tracleer® and tacrolimus or sirolimus is not recommended. Patients who require this combination must be closely monitored for undesirable effects from Tracleer® and with respect to the blood concentrations of tacrolimus or sirolimus.

Glibenclamide: simultaneous administration of twice daily 125 mg Tracleer® for 5 days decreased the plasma concentrations of glibenclamide (a CYP3A4 substrate) by 40%, possibly with significantly reduced hypoglycaemic activity. The plasma concentrations of bosentan were reduced by 29%. Moreover, the incidence of increases in aminotransferase was raised in these patients. Both glibenclamide and bosentan inhibit the bile salt export pump, which might explain the increases in aminotransferase values. Therefore, this combination should not be used (see section on «Contraindications»). There are no data on interactions with other sulfonylureas.

Warfarin: simultaneous administration of Tracleer® (500 mg twice daily) led to a decrease in the plasma concentrations of S-warfarin (a CYP2C9 substrate) and of R-warfarin (a CYP3A4 substrate) by ca. 30%. In patients with pulmonary arterial hypertension chronically treated with warfarin, administration of 125 mg Tracleer® twice daily had no clinically relevant effect on the prothrombin time/INR. It is not necessary to adjust the dose of warfarin or similar anticoagulants at the start of treatment with bosentan. However, close monitoring of the INR is recommended, particularly at the start of treatment and when the dose is titrated up.

Simvastatin: simultaneous administration of 125 mg Tracleer® twice daily for 5 days reduced the plasma concentrations of simvastatin (a CYP3A4 substrate) and its active ß-hydroxy acid metabolite by 34% and 46% respectively. Plasma concentrations of bosentan were unaffected by simultaneous administration of simvastatin. The possibility should be considered of monitoring the cholesterol values, followed by dose adjustment of simvastatin.

Ketoconazole: simultaneous administration of 62.5 mg Tracleer® twice daily for 6 days and ketoconazole, a strong CYP3A4 inhibitor, approximately doubled the plasma concentrations of bosentan. Dose adjustment of Tracleer® is not necessary. Although this has not been demonstrated with *in vivo* studies, it is to be expected that other potent inhibitors of CYP3A4 (e.g. itraconazole and ritonavir) will cause similar increases in the plasma concentrations of bosentan. Nevertheless, the risk exists that patients who are poor CYP2C9 metabolisers and who are simultaneously administered a CYP3A4 inhibitor may develop further increases in concentrations of bosentan, which might lead to dangerous adverse effects.

Digoxin: simultaneous administration of 500 mg bosentan twice daily for 7 days caused reductions in the AUC for digoxin by 12%, the C_{max} by 9% and the C_{min} by 23%. These effects may be linked to induction of P-glycoprotein. This interaction probably has no clinical relevance.

Rifampicin: rifampicin is a potent inducer of CYP2C9 and CYP3A4. Simultaneous administration of rifampicin and Tracleer® 125 mg (2x daily for 7 days) reduces the plasma concentration of bosentan by 58%. The reduced efficacy of bosentan must be considered.

Sildenafil: simultaneous administration of Tracleer® 125 mg 2x daily with sildenafil 80 mg 3x daily results in a decrease of 63% in the AUC for sildenafil and an increase of 50% in the AUC for bosentan. The combination is well tolerated. It is not thought to be necessary to adjust the dose of Tracleer®.

Tadalafil: After several doses of the co-administration of bosentan (125 mg twice daily) and tadalafil (40 mg once daily), bosentan decreased the systemic availability of tadalafil by 42 % and decreased Cmax of tadalafil by 27 %. Tadalafil did not affect the availability (AUC and Cmax) of bosentan or its metabolites.

Lopinavir+Ritonavir: Co-administration of Tracleer® 125 mg twice daily and lopinavir+ritonavir 400+100mg twice daily during 9.5 days in healthy volunteers, resulted at day 4 in plasma concentrations of bosentan that were approximately 48-fold higher than those measured after Tracleer® administered alone. On day 10, plasma concentrations of bosentan were approximately 5-fold higher than with Tracleer® administered alone. Plasma concentrations at steady state of lopinavir and ritonavir were decreased by approximately 14% and 17%, respectively. When administered concomitantly with lopinavir+ritonavir or other ritonavir-boosted protease inhibitors, the patient's tolerability of Tracleer® and the HIV therapy should be monitored (see section on «Special warnings and precautions for use»).

Due to the marked hepatotoxicity of nevirapine, which could increase bosentan liver toxicity, this combination is not recommended.

Pregnancy and lactation
Pregnancy
Reproduction toxicity was found in animal experiments (for teratogenicity, embryotoxicity; see section on «Preclinical safety data»). There are only a few post-marketing reports on the use of Tracleer® in pregnant women. Tracleer® is contraindicated during pregnancy (see section on «Contraindications»).
Tracleer® may only be used in women of child-bearing age if the pregnancy test was negative before the start of treatment, if adequate advice has been given on reliable contraceptive methods and if they have started to employ a reliable contraceptive method. Patients and the prescribing doctor should be informed that Tracleer® can reduce the efficacy of hormonal contraceptives due to a potential pharmacokinetic interaction (see section on «Interactions »). For this reason, women of child-bearing age may not use hormonal contraception (oral, intramuscular, transdermal, vaginal and implantable forms) as their sole method of contraception, but must use an additional or alternative reliable contraceptive method (female condom, diaphragm, intrauterine pessary, use of a condom by the partner). A consultation with a

gynaecologist should be considered if there are any doubts on the contraceptive advice given to an individual patient. Contraception should be continued for three months after discontinuation of treatment with Tracleer®.
Due to the possible failure of hormonal contraception during treatment with Tracleer® and given the risk of a severe deterioration of pulmonary hypertension during a pregnancy, monthly pregnancy tests are recommended during treatment with Tracleer® to ensure that pregnancy is detected as early as possible. Women who become pregnant during treatment with Tracleer® should be informed of the potential risk to the foetus.

Lactation
It is unknown whether bosentan passes into breast milk. Breast-feeding mothers treated with Tracleer® should stop breastfeeding.

Fertility
Animal experiments have shown testicular effects (see also section preclinical data). In a clinical study investigating the effects of bosentan on testicular function in male PAH patients, 6 out of 24 subjects (25%) had a decreased sperm concentration of at least 50% from baseline value at 6 months of treatment with bosentan. Based on these findings and preclinical data, it cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men. In male children, a long-term influence on fertility after treatment with bosentan cannot be excluded.

Effects on ability to drive and use machines
No studies have been performed on the effects of Tracleer® on the ability to drive and use machines. Because of the possible undesirable effects, caution is necessary when driving or using machines.

Undesirable effects
Summary of results from placebo-controlled trials
In 20 placebo-controlled studies, conducted in a variety of therapeutic indications, a total of 2,486 patients were treated with bosentan at daily doses ranging from 100 mg to 2000 mg and 1,838 patients were treated with placebo. The mean treatment duration was 45 weeks. The most commonly reported adverse drug reactions (as occurring in at least 1% of patients on bosentan and at a frequency at least 0.5% more than on placebo) are headache (11.5% vs 9.8%), oedema/fluid retention (13.2% vs 10.9%), abnormal liver function test (10.9% vs 4.6%) and anaemia/haemoglobin decrease (9.9% vs 4.9%).

Treatment with bosentan has been associated with dose-dependent elevations in liver aminotransferases and decreases in haemoglobin concentration (see section Special warnings and precautions for use).

Adverse reactions/undesirable effects in 20 placebo-controlled studies with bosentan are ranked according to frequency using the following convention: very common (≥ 1/10); common (≥1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).—Reports from post-marketing experience are included in *Italics*, with frequency categories based on adverse event reporting rates on bosentan in the 20 placebo-controlled studies.

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. No clinically relevant differences in undesirable effects were observed between the overall dataset and the approved indications.

System organ class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorders	Common	Anaemia, haemoglobin decrease, (see section 4.4)
	Not known[1]	*Anaemia or haemoglobin decreases requiring red blood cell transfusion*
	Uncommon	*Thrombocytopenia*
	Uncommon	*Neutropenia, leukopenia*
Immune system disorders	Common	Hypersensitivity reactions (including dermatitis, pruritus and rash)[2]
	Rare	*Anaphylaxis and/or angioedema*
Nervous system disorders	Very common	Headache[3],
	Common	*Syncope[4]*
Cardiac disorders	Common	*Palpitations[4]*
Vascular disorders	Common	Flushing
	Common	*Hypotension[4]*
Respiratory thoracic and mediastinal disorders	Common	*Nasal congestion*
Gastrointestinal disorders	Common	Gastrooesophageal reflux disease Diarrhoea
Hepatobiliary disorders	Very common	Abnormal liver function test , («Special warnings and precautions for use»)
	Uncommon	*Aminotransferase elevations associated with hepatitis and/or jaundice* («Special warnings and precautions for use»)
	Rare	*Liver cirrhosis, liver failure*
Skin and subcutaneous disorders	Common	Erythema
General disorders and administration site conditions	Very common	Oedema, fluid retention[5]

[1] Frequency cannot be estimated from the available data.
[2] Hypersensitivity reactions were reported in 9.9% of patients on bosentan and 9.1% of patients on placebo.
[3] Headache was reported in 11.5% of patients on bosentan and 9.8% of patients on placebo.
[4] These types of reactions can also be related to the underlying disease.

[5] Oedema or fluid retention was reported in 13.2% of patients on bosentan and 10.9% of patients on placebo.

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 «Special warnings and precautions for use»)).

Uncontrolled studies in paediatric patients
The safety profile in a pediatric study performed with the film-coated tablet (n = 19, median age 10 years [range 3–15 years], open-label bosentan 2 mg/kg twice daily; treatment duration 12 weeks) was similar to that observed in the pivotal trials in adult patients with PAH.

In this study, the most frequent adverse events were flushing (21%), headache, and abnormal liver function test (each 16%).

Laboratory abnormalities
Liver test abnormalities
In the clinical programme, dose-dependent elevations in liver aminotransferases generally occurred within the first 26 weeks of treatment, usually developed gradually, and were mainly asymptomatic. In the post-marketing period rare cases of liver cirrhosis and liver failure have been reported.

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 («Special warnings and precautions for use»)).

In the 20 integrated placebo-controlled studies, elevations in liver aminotransferases $\geq$ 3 times the upper limit of normal (ULN) were observed in 11.2% of the bosentan-treated patients as compared to 2.4% of the placebo-treated patients. Elevations to $\geq 8 \times$ ULN were seen in 3.6% of the bosentan-treated patients and 0.4% of the placebo-treated patients. Elevations in aminotransferases were associated with elevated bilirubin ($\geq 2 \times$ ULN) without evidence of biliary obstruction in 0.2% (5 patients) on bosentan and 0.3% (6 patients) on placebo.

Haemoglobin
In 20 integrated placebo-controlled studies in adult patients, a decrease in haemoglobin concentration to below 10 g/dL from baseline was reported in 8.0% of bosentan-treated patients and 3.9% of placebo-treated patients (see section «Special warnings and precautions for use»).

In the pooled analysis of pediatric studies conducted in PAH, a decrease in hemoglobin concentration to below 10 g/dL from baseline was reported in 10.0% of patients. There was no decrease to below 8 g/dL.

Overdose
Bosentan has been administered to healthy volunteers as single doses of up to 2400 mg and to patients with diseases other than pulmonary hypertension at dosages of up to 2000 mg/day for two months. The most frequent undesired effects were mild to moderate headache. A massive overdose could lead to marked hypotension, which would necessitate supportive cardiovascular measures. In the post-marketing period, an overdose of 10,000 mg bosentan was reported in an adolescent male patient. He exhibited symptoms of nausea, vomiting, hypotension, dizziness, perspiration and blurred vision. He made a full recovery within 24 hours with blood pressure support. Dialysis cannot be carried out in cases of bosentan overdoses.

Pharmacological properties
ATC Code: C02KX01

Mechanism of action
Bosentan is a dual endothelin receptor antagonist (ERA), with affinity for both ET_A and ET_B receptors. Bosentan reduces both pulmonary and systemic vascular resistance, thus increasing the cardiac output, without raising the heart rate.
The neurohormone endothelin-1 (ET-1) is one of the most potent known vasoconstrictors. It can also enhance fibrosis, cell proliferation, cardiac hypertrophy and remodelling and is pro-inflammatory. These effects are mediated by the binding of endothelin to ET_A and ET_B receptors, which are localised in the endothelium and in the cells of vascular smooth muscle. The ET-1 concentrations in tissue and plasma are increased in some cardiovascular disturbances and connective tissue diseases, including pulmonary arterial hypertension, scleroderma, acute and chronic heart failure, myocardial ischaemia and arteriosclerosis, indicating that ET-1 play a pathogenetic role in these conditions. In the absence of endothelin receptor antagonists, increased ET-1 concentrations are closely correlated with the severity and prognosis of pulmonary arterial hypertension and heart failure.
Bosentan is a competitive inhibitor of endothelin binding to ET_A and ET_B receptors, with somewhat higher affinity to ET_A receptors (K_i = 4.1-43 nM) than to ET_B receptors (K_i = 38-730 nM). Bosentan is a specific antagonist of ET receptors and does not bind to other receptors.

Pharmacodynamic properties
In animal models of pulmonary hypertension, chronic oral administration of bosentan leads to a reduction in pulmonary vascular resistance and to decreases in pulmonary vascular and right ventricular hypertrophy. In an animal model of pulmonary fibrosis, bosentan caused a reduction in collagen deposition in the lungs.

Clinical efficacy

Pulmonary arterial hypertension (PAH)
Two randomised, double blind, multicentre placebo-controlled trials were performed with 32 (trial AC-052-351) or 213 (trial AC-052-352, BREATHE-1) patients with pulmonary arterial hypertension with functional severity corresponding to WHO Classes III-IV (primary pulmonary hypertension or secondary pulmonary hypertension, predominantly linked to scleroderma). After 4 weeks of treatment with 62.5 mg Tracleer® twice daily, the maintenance doses investigated in these trials were 125 mg Tracleer® twice daily in AC-052-351 and 125 mg and 250 mg twice daily in AC-052-352.

Tracleer® was added to the patients' current therapy, which could contain a combination of anticoagulants, vasodilators (e.g. calcium antagonists), diuretics, oxygen and digoxin, but not epoprostenol. The control group was given placebo in addition to current therapy.
The primary end point of each trial was the change in the 6 min walking range - after 12 weeks in the first trial and after 16 weeks in the second. Treatment with Tracleer® significantly improved physical performance in both trials. The placebo-corrected increases in the walking range, in comparison to the initial value at the start of the trial were 76 m (p= 0.02; t-Test) and 44 m (p= 0.0002; Mann-Whitney U-test), measured at the time point for the primary end point for each trial. The differences between the two groups - with twice daily doses of 125 mg or 250 mg - were not statistically significant, although there was a trend to better physical performance with the higher dosage.
The improvement in the walking range was evident after 4 weeks of treatment, was marked after 8 weeks of treatment and was maintained up to 28 weeks double blind treatment, as performed on some of the patients.
A retrospective responder analysis was performed in these placebo-controlled trials for the 95 patients assigned to the treatment with twice daily 125 mg Tracleer® - on the basis of the change in the walking range, the functional WHO class and the dyspnoea. This gave the following results: At week 8, 66 patients exhibited improvement, 22 patients were stable and 7 patients deteriorated. Of the 22 patients who were stable in week 8, 6 improved at week 12/16 relative to the initial value, while 4 deteriorated. Of the 7 patients with deterioration in week 8, 3 improved at week 12/16 relative to the initial value, while 4 deteriorated.
Invasive haemodynamic parameters were only evaluated in the first trial. Treatment with Tracleer® led to a clear increase in the cardiac index, associated with significant reductions in pulmonary arterial pressure, pulmonary vascular resistance and mean right atrial pressure.
Treatment with Tracleer® led to reduction in the symptoms of pulmonary arterial hypertension and to improvement in physical performance. Dyspnoea (measured during the walking test) improved in the patients treated with Tracleer®. At the start of trial AC-052-352, 92% of the 213 patients were categorised as being in WHO class III for functional severity and 8% in class IV. Treatment with Tracleer® led to an improvement in the functional severity class for 42.4% patients, in comparison with 30.4% for placebo. In both trials, the total change in functional WHO class was significantly better with the Tracleer® patients than with the placebo patients. Treatment with Tracleer® was associated with a significant reduction in the frequency of clinical deterioration after 28 weeks, in comparison to placebo (10.7% vs. 37.1%; p= 0.0015).

In a randomised, double-blind, multicentre, placebo-controlled trial, 185 patients with mild symptomatic PAH in functional class II (mean walking range of 6 minutes at a baseline of 443 m) were given 62.5 mg bosentan twice daily for 4 weeks, followed by 125 mg twice daily (n=93) or placebo (n=92) for 6 months. The patients were not undergoing any specific treatment (n=156) or were on a stable dose of sildenafil (n=29). The co-primary endpoints were the changes in PVR (pulmonary vascular resistance) and the placebo-controlled 6-minute walking range over the duration of 6 months. The time to clinical deterioration (death, hospitalization due to PAH complications or symptomatic deterioration in PAH), Borg Dyspnoea Index, change in the WHO functional class and haemodynamics were evaluated as secondary

endpoints. After 6 months, the placebo-controlled reduction in PVR was 22.6% ($p < 0.0001$). The improvement in the mean 6-minute walking range in the bosentan group compared with the placebo group was 13.8 m ($p = 0.0758$). With reference to changes in PVR, no significant differences were found for the subgroups secondary PAH associated with HIV, congenital heart disease, connective tissue disease or combination therapy with sildenafil due to the small numbers of patients.

Clinical deterioration was significantly delayed under bosentan when compared with placebo (relative risk reduction of 77.3%, $p = 0.0114$). Bosentan reduced the incidence of a deterioration by at least 1 functional class (3.4% bosentan vs. 13.2% placebo, p=0.0285) and improved the haemodynamics (mPAP, TPR, Cardiac Index and SVO2; $p < 0.05$).

In a prospective, multicentre, randomised, double blind, placebo-controlled trial (BREATHE-5) in patients with PAH of WHO class III linked to congenital heart disease and Eisenmenger physiology, Tracleer® (n=37) or placebo (n=17) were administered for 16 weeks with the same dosage regimen as in the pivotal trials. The primary end point was to demonstrate that Tracleer® treatment does not exacerbate hypoxaemia. After 16 weeks, Tracleer® improved oxygen saturation by 1% (95% CI -0.7: 2.8%) in comparison to placebo. This shows that bosentan does not exacerbate hypoxaemia. Treatment with Tracleer® led to a significant reduction in pulmonary vascular resistance and improved physical performance. After 16 weeks, the placebo-controlled increase in the 6-min walking range was 53 m (p=0.0079).

Patients with PAH associated with HIV infection were not included in the pivotal trials (trials AC-052-351 and BREATHE-1). In a multicentre, open, non-comparative trial (BREATHE-4), 16 patients with PAH (WHO classes III and IV) associated with HIV infection were treated with the same dosage scheme as in the pivotal trials. After 16 weeks, there were significant improvements in the physical performance and in cardiopulmonary haemodynamics, in comparison with the initial values. The WHO function class was improved in 14 patients. Most patients (15/16) were under stable antiretroviral therapy with nucleoside or non-nucleoside reverse transcriptase inhibitors, plus a protease inhibitor - the most frequently used combination therapy. Tracleer® had no evident effect on the control parameters for HIV infection during the trial - such as the count of CD4 cells or the HIV-1 RNA titre.

Clinical efficacy in children and adolescents with pulmonary arterial hypertension
One trial has been performed in children with pulmonary arterial hypertension. Tracleer® was investigated in an open uncontrolled trial in 19 paediatric patients with pulmonary arterial hypertension (AC-052-356, BREATHE-3: 10 patients with primary pulmonary hypertension, 9 patients with pulmonary arterial hypertension from congenital heart defects). The trial was largely designed to record pharmacokinetic parameters (see «Pharmacokinetic properties»). The patients were divided into three equal groups of different weights (see «Dosage in children and adolescents») and treated for 12 weeks. At the time when the trial was started, half of the patients in each group were being given intravenous epoprostenol. The epoprostenol dose remained constant throughout the trial. The age range was 3-15 years. At the start of the trial, all patients were either of WHO class II (N= 15 patients, 79%) or class III (N= 4 patients, 21%).
Haemodynamic parameters were measured in 17 patients. Relative to the initial values, the cardiac index increased by a mean of 0.5 l/min/m², the mean pulmonary

arterial pressure decreased by 8 mmHg and the pulmonary vascular resistance decreased by 389 dyn·sec·cm^{-5}. The improvements in haemodynamic parameters relative to the initial values occurred either with or without simultaneous administration of epoprostenol. The changes in exercise test parameters in week 12 relative to the initial value were very variable and were not statistically significant.

Long-term survival rate in pulmonary arterial hypertension
The long-term survival rate was recorded for all 235 Tracleer® patients in the two main placebo-controlled trials (AC-052-351 and AC-052-352) and their open trial extensions (AC-052-353 and AC-052-354). The mean duration of bosentan administration was 1.9 ± 0.7 years (min: 0.1; max: 3.3 years) and the patients were monitored for a mean of 2.0 ± 0.6 years. Most of the patients had been diagnosed with primary pulmonary hypertension (PPH; 72%) and were assigned to WHO function class III (84%). The survival rate of the whole population after 1 year of treatment with Tracleer® was 93% and after 2 years 84% (Kaplan-Meyer). The survival rate in the subgroup with primary PAH after both 1 year and 2 years was higher - 96% and 89%, respectively. Comparison with the data for epoprostenol patients from six specialised treatment centres (N= 682) showed that Tracleer® improves the survival rate of patients with pulmonary arterial hypertension at least as well as epoprostenol does.

Systemic sclerosis with active digital ulcer disease
Two randomised, double blind, multicentre, placebo-controlled trials have been performed with 122 (RAPIDS-1) and 190 (RAPIDS-2) adult patients with systemic sclerosis and active digital ulcer disease - including both current digital ulcer and a history of digital ulcer within the preceding year. In the RAPIDS-2 trial, the patients exhibited at least one new digital ulcer and, in both trials together, 85% of patients had at least one digital ulcer on inclusion. After 4 weeks of 62.5 mg Tracleer® twice daily, the maintenance dose in both trials was 2 x 125 mg daily. The double blind treatment lasted for 16 weeks (RAPIDS-1) or 24 weeks (RAPIDS-2). Basic treatment of systemic sclerosis and digital ulcer was allowed if this remained constant for at least 1 month before and during the double blind trial phase.
In both trials, the number of new digital ulcers between inclusion and the end of the trial was a primary end point.
Treatment with Tracleer® resulted in fewer new digital ulcers during therapy than with placebo. In the RAPIDS-1 trial, the patients treated with bosentan developed a mean of 1.4 new digital ulcers during the 16 weeks of double blind treatment, in comparison with 2.7 in the placebo group (p=0.0042). The corresponding values in the RAPIDS-2 trial were 1.9 or 2.7 new digital ulcers (p= 0.0351) during the 24 week double blind treatment. In both trials, the patients treated with bosentan developed fewer multiple new digital ulcers during the trial than in the placebo group and it lasted longer before a new digital ulcer could be developed.
Although the effect of bosentan on the reduction in the number of new digital ulcers was independent of the initial number of digital ulcers, the efficacy was greater in patients with multiple digital ulcers.

The efficacy of bosentan on the healing of digital ulcers was investigated as secondary end point in the RAPIDS-1 trial and as co-primary end point in the RAPIDS-2 trial. No effect of bosentan was found in either trial.

Pharmacokinetic properties
Pharmacokinetic data are available after oral and intravenous administration to adult patients with pulmonary arterial hypertension. The data show that the systemic bioavailability of bosentan in adult patients with pulmonary arterial hypertension is about 2-fold higher than in healthy adult volunteers.
The pharmacokinetics of bosentan are dose- and time-dependent in healthy adults. Clearance and volume of distribution decrease with increasing intravenous dose, but then later increase. After oral administration, the systemic availability is dose-proportional up to 500 mg. At higher oral doses, the increases in C_{max} and AUC are less than dose proportional.

Absorption
After an oral dose of 125 mg to healthy volunteers, the absolute bioavailability of bosentan is ca. 50%. This is not impaired by food intake. At this dosage, maximal plasma concentrations are reached within 3-5 hours.

Distribution
Bosentan is strongly bound (>98%) to plasma proteins, mainly to albumin. Bosentan does not penetrate into erythrocytes. The volume of distribution (V_{ss}) of about 18 L was determined after intravenous administration of 250 mg.

Metabolism and elimination
After intravenous administration of a single dose of 250 mg, the clearance is ca. 9 l/h. The terminal elimination half-life ($t_{½}$) is 5.4 h.
After repeated administration, the plasma concentrations gradually decrease to 50-65% of the concentrations after a single administration. This decrease is probably due to autoinduction of the hepatic metabolic enzymes. Steady-state conditions are reached within 3-5 days.
Bosentan is metabolised in the liver by the cytochrome P450 isoenzymes CYP3A4 and CYP2C9 and then eliminated in the bile. Less than 3% of an oral dose appears in the urine.
Bosentan forms three metabolites. Only one of these is pharmacologically active and accounts for up to 20% of bosentan's activity.
Bosentan induces CYP2C9 and CYP3A4, possibly also CYP2C19 and P-glycoprotein. *In vitro,* bosentan inhibits the bile salt export pump in hepatocytes.
In vitro data show that bosentan has no relevant inhibitory effect on the following cytochrome isoenzymes: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 3A4. It is therefore not to be expected that bosentan will cause an increase in the plasma concentrations of drugs metabolised by these isoenzymes.

Kinetics in special patient groups

Sex, body weight, race, age
The available data indicate that it is not to be expected that gender, body weight, race or age has any relevant effect on the pharmacokinetics of bosentan in adults.

Children and adolescents
The pharmacokinetics after administration of single and multiple doses were examined in children and adolescents with pulmonary arterial hypertension, dosed according to body weight (BREATHE-3 see sections on «Pharmacological

properties»). The systemic availability of bosentan decreased with time, as is compatible with the known enzyme induction by bosentan.
The mean AUC (CV%) for bosentan in children treated with 31.25, 62.5 or 125 mg twice daily was calculated as 3496 (49), 5428 (79), and 6124 (27) ng·h/ml, respectively. This was lower than the value of 8149 (47) ng·h/ml for adult patients with pulmonary arterial hypertension given 125 mg twice daily. At steady state, the systemic bioavailability in the different weight classes relative to the bioavailability in adults were as follows: 10-20 kg, 43%; 20-40 kg, 67%; >40 kg, 75%. The reason for this difference is unclear and may be linked to increased hepatic metabolism and elimination. Moreover, ca. 50% of the children had a heart defect, so that the haemodynamics were changed, which could influence the pharmacokinetics.
It is unclear whether this could affect the hepatotoxicity. Gender and simultaneous administration of intravenous epoprostenol had no significant effect on the pharmacokinetic properties of bosentan. No pharmacokinetic data are available for children aged under 3 years.

Liver disorders
No relevant changes in pharmacokinetics were observed in patients with slightly impaired liver function (Child-Pugh class A). In these patients, the area under the concentration-time curve at steady state was increased by 9% for bosentan and by 33% for the main metabolite Ro 48-5033, in comparison with healthy volunteers. The pharmacokinetics of bosentan have not been investigated in patients with liver disorders corresponding to Child-Pugh classes B or C.

Renal disorders
In patients with severe renal disorders (creatinine clearance 15-30 ml/min.), the plasma concentrations of bosentan were about 10% lower. The plasma concentrations of the bosentan metabolite were approximately doubled in comparison to volunteers with normal renal function. There has been no specific experience with dialysis patients. Because of bosentan's physicochemical properties and the high proportion bound to plasma protein, it cannot be assumed that any significant proportion of bosentan will be removed from the systemic circulation by dialysis (see section on «Posology and method of administration»).

Preclinical safety data

Repeat dose toxicity
There is evidence for mild disorders of the thyroid hormones after administration of bosentan to rats. On the other hand, there is no evidence that bosentan impairs thyroid function in man (thyroxine, TSH). Treatment with bosentan led to allergic reactions in two predictive models in the guinea pig for detecting allergenic potential (types I and IV). In both models, allergic reactions were only observed after simultaneous application of adjuvant. No allergic reactions were observed in a mouse model for type 1 allergies. The effect of bosentan on mitochondrial function is unknown.

Genotoxicity
Bosentan was negative in tests for genotoxicity.

Carcinogenicity
A 2-year carcinogenicity study has been performed in the mouse model, with plasma concentrations about 2- to 4-fold higher than after a therapeutic dose in man. These found an increase in the combined incidence of hepatocellular adenomas and carcinomas in male mice, but not in female mice. In the rat model, oral administration of bosentan for 2 years led to a slight but significant increase in the combined incidence of follicular adenomas and carcinomas of the thyroid, in male, but not in female rats. The plasma concentrations in this study were 9- to 14-fold greater than the plasma concentrations after a therapeutic dose in man.

Reproductive toxicity
Bosentan has been shown to be teratogenic in the rat at plasma concentrations 1.5-fold greater than the plasma concentrations after a therapeutic dose in man.
Teratogenic effects, including congenital malformation of the head, face and major vessels, were dose dependent. The similarities with the malformations found with other ET receptor antagonists and those in ET-knock-out mice indicate that this is a class effect. Proper precautions must be taken in women of child-bearing age (see sections on «Contraindications», «Pregnancy and lactation»).
Fertility studies have been performed in male and female rats at plasma concentrations which were 21-fold to 43-fold greater than the expected range after a therapeutic dose in man. No effects were found on sperm count, sperm motility, sperm vitality, mating behaviour or fertility. There were also no undesired effects on the development of the embryo before implantation or on the implantation itself.

Slightly increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the maximum recommended human dose [MRHD] and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months.

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

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

Other comments
Expiry date
The preparation may only be used up to the date marked on the container with «EXP».

Special storage conditions
Store below 25°C. Keep out of the sight and reach of children.

Packs
Tracleer® 62.5 mg: 60 Film-Coated Tablets
Tracleer® 125 mg: 60 Film-Coated Tablets

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