Pediatr Drugs 2010; 12 (1): 63-73
1174-5878/10/0001-0063/$49.95/0

Bosentan

In Pediatric Patients with Pulmonary Arterial Hypertension

Natalie J. Carter and *Gillian M. Keating*

Adis, a Wolters Kluwer Business, Auckland, New Zealand

Contents

Abstract

Bosentan is a dual endothelin-1 (ET-1) receptor antagonist that has affinity for ET-1 receptors A and B. In the EU, oral bosentan (Tracleer®) is indicated to improve exercise capacity and symptoms in patients with pulmonary arterial hypertension (PAH) of WHO functional class III; benefits have also been seen in patients with WHO functional class II PAH. Bosentan is available as film-coated tablets, and a new dispersible formulation of bosentan has also recently been approved in the EU for the treatment of PAH in children aged ≥2 years.

A noncomparative, multicenter, phase III trial (FUTURE-1), which was primarily designed to investigate the pharmacokinetics of dispersible bosentan in pediatric patients, demonstrated that increasing the dosage of bosentan from 2 to 4 mg/kg twice daily was unlikely to result in increased exposure to bosentan.

Exploratory measures of efficacy in FUTURE-1 demonstrated that target dosages of twice-daily dispersible bosentan 4 mg/kg (in patients weighing <30 kg) or 120 mg (in patients weighing ≥30 kg) for 12 weeks were beneficial in pediatric patients (aged ≥2 to <12 years) with WHO functional class II or III PAH.

Film-coated bosentan 31.25, 62.5, or 125 mg (in pediatric patients weighing 10–20, >20–40, or >40 kg, respectively) twice daily for 12 weeks significantly ($p < 0.05$) improved the majority of hemodynamic measures evaluated as an exploratory measure in pediatric patients (aged 3–15 years) with WHO functional class II or III PAH in another noncomparative, multicenter, pharmacokinetic trial (BREATHE-3). However, there was no significant change in peak oxygen consumption or mean walk distance in those patients capable (i.e. children aged ≥8 years) of performing the 6-minute walk test.

Bosentan was generally well tolerated in clinical trials of pediatric patients with PAH, with most adverse events being mild or moderate in severity and resolving with continued treatment.

Features and properties of oral bosentan (Tracleer®)	
EU indication	
To improve exercise capacity and symptoms in patients (pts) with pulmonary arterial hypertension (PAH) of WHO functional class III; benefits have also been seen in WHO class II PAH patients. A dispersible formulation of bosentan is approved in the EU for use in children aged ≥2 years with PAH	
Mechanism of action	
Dual endothelin-1 receptor antagonist	
Dosage and administration	
The optimal dose of bosentan in pediatric pts has not been clearly defined; however, because clinical trials have shown that increasing the dose of bosentan from 2 to 4 mg/kg does not result in increased bosentan exposure in pediatric pts, the higher dose is unlikely to result in greater efficacy in this pt population	
Frequency	Twice daily
Route of administration	Oral
Steady-state pharmacokinetic profile of dispersible (DIS) bosentan (BOS) 2 or 4 mg/kg twice daily (n = 35) and film-coated (FIL) BOS 31.25, 62.5, or 125 mg twice daily (n = 18) in pediatric pts with PAH	
Geometric mean peak plasma concentration [C_{max}] (ng/mL)	DIS BOS 2: 583; 4: 649 FIL BOS 31.25: 685; 62.5: 1136; 125: 1200
Geometric mean area under the concentration-time curve during a dosage interval (ng • h/mL)	DIS BOS 2: 3577; 4: 3371 FIL BOS 31.25: 3496; 62.5: 5428; 125: 6124
Median time to C_{max} (h)	DIS BOS 2: 3.0; 4: 3.0 FIL BOS 31.25: 2.5; 62.5: 1.0; 125: 1.8
Adverse events occurring in >6% of pediatric pts in BOS clinical trials	
DIS BOS	Abdominal pain, vomiting
FIL BOS	Flushing, edema, headache, increased ALT and/or AST levels

Pulmonary arterial hypertension (PAH) is a chronic, multifactorial disease that involves vasoconstriction, remodeling of pulmonary arterial walls and thrombosis *in situ*, leading to increased pulmonary vascular resistance, right ventricular hypertrophy, and, when advanced, right heart failure and death.[1-4] PAH falls into the hemodynamic subgroup of pre-capillary pulmonary hypertension, which is defined as a mean pulmonary arterial pressure ≥25 mmHg, a pulmonary wedge pressure ≤15 mmHg, and normal or reduced cardiac output (all determined at rest).[1]

Pulmonary hypertension in children is similar to that in adults, although children have a poorer prognosis than adults when left untreated (survival estimate <1 vs 2.8 year[s][5,6]), and may be more unwell than adults at first presentation.[1] Although pulmonary hypertension of all types have been described in pediatric patients, the majority of children present with idiopathic (formerly known as primary[3]) or heritable (formerly known as familial[1]) pulmonary hypertension, or pulmonary hypertension associated with congenital heart disease (CHD).[1]

Lung or heart-lung transplant remains the only curative treatment for PAH.[1,3] However, development of PAH-specific drugs (i.e. endothelin receptor antagonists [e.g. ambrisentan, bosentan, and sitaxentan], phosphodiesterase type-5 inhibitors [e.g. sildenafil and tadalafil], and prostanoid/prostacyclin agonists [e.g. beraprost, epoprostenol, iloprost, and treprostinil]) has improved the outlook for patients with PAH in terms of survival rates,[1,7] symptomatic status, rate of clinical deterioration, and hospitalization rates.[1] The aim of these agents is to vasodilate pulmonary vasculature and reverse the remodeling of pulmonary arterial walls by targeting the endothelin, nitric oxide, or prostacyclin signaling pathways.[8]

In the EU, PAH-specific drugs are recommended for use in patients with nonvasoreactive PAH (i.e. nonresponders to vasoactivity testing) and in those with vasoreactive PAH (i.e. responders to vasoactivity testing) who do not demonstrate a sustained response to calcium channel antagonists or who remain in, or progress to, WHO functional class III PAH.[1] Ambrisentan, bosentan, sildenafil, sitaxentan, and tadalafil are recommended for use in adults with WHO functional class II PAH who meet these criteria; beraprost, epoprostenol, iloprost, and treprostinil are also recommended options in such patients with WHO functional class III PAH.[1] According to WHO criteria, patients with class II or III PAH are comfortable at rest, but have a slight (class II) or marked (class III) limitation in physical activity, with ordinary (class II) or less than ordinary (class III) activity causing undue dyspnea or fatigue, chest pain, or near syncope.[1]

Treatment recommendations for pediatric patients with WHO functional class II or III PAH who meet treatment criteria for PAH-specific drugs are similar to those for adults, although there is less supporting evidence.[1] Bosentan (Tracleer®), a dual endothelin-1 (ET-1) receptor antagonist available as film-coated and dispersible tablets, is one of the few PAH-specific drugs that have been studied in the pediatric population. The new dispersible tablet formulation of bosentan, which was specifically designed for use in pediatric patients, has recently been approved in the EU.[9] It should be noted that the *in vivo* bioavailability of the two formulations has not yet been compared.[10] ET-1 is a neurohormone that is predominantly released from vascular endothelium and, among other functions, is one of the most potent vasoconstrictors known.[11] Plasma and tissue levels of ET-1 are increased in patients with PAH,[10-12] primarily because of increased ET-1 synthesis.[11]

The use of oral bosentan in adult patients with PAH[13-15] or systemic sclerosis-related digital ulcers[14,16] has been reviewed previously. This profile reviews, from an EU perspective, the pharmacologic properties of oral bosentan and its clinical efficacy and tolerability in pediatric patients with PAH. Where pediatric data are unavailable, data pertaining to the use of bosentan in adults are discussed. Medical literature on the use of bosentan in pediatric patients with PAH was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

This section provides a brief overview of the pharmacodynamics of bosentan, which have been extensively reviewed elsewhere.[13-17]

- Bosentan is a dual ET-1 receptor antagonist, which binds specifically and competitively to ET-1 receptors A (ET_A) and B (ET_B), thereby antagonizing the binding of ET-1.[18] In patients with PAH, plasma ET-1 levels were significantly ($p < 0.01$) increased from baseline by 2-fold after a single dose of bosentan, possibly as a result of bosentan-associated displacement of ET-1 from ET_B receptors.[19]
- Treatment with bosentan improved several cardiopulmonary hemodynamic variables (e.g. systemic and pulmonary vascular resistance and mean pulmonary artery pressure) in patients with PAH,[13,14] including pediatric patients participating in the BREATHE (Bosentan Randomized trial of Endothelin Antagonist THErapy for pulmonary hypertension)-3 trial[20] (section 3).
- Relative to placebo, bosentan significantly ($p < 0.001$) improved brachial artery endothelial function (determined by ultrasound-derived, flow-mediated dilation) in adults ($n = 7$) who had systemic sclerosis with PAH and/or digital ulcers and endothelial dysfunction at baseline.[21] In addition, mean systolic pulmonary

pressure was reduced to a significant ($p < 0.004$) extent from baseline to study end in all patients;[21] arterial blood pressure and endothelium-independent vascular function were not significantly affected by bosentan.

- In adult patients with various types of PAH, bosentan was associated with a reduction in plasma N-terminal-prohormone-brain natriuretic peptide (NT-proBNP) levels (a surrogate marker that is considered predictive of survival), a reduction in endothelial cell activation, restoration of endothelial cell or T-cell function, immunomodulation, and increased serum interleukin-12 levels (a cytokine that induces T helper [T_h]-1 cell differentiation and reduces T_h-2 activity) [reviewed by Dhillon and Keating[13]].
- One years' treatment with bosentan significantly ($p < 0.05$) increased serum matrix metalloproteinase (MMP)-9 levels,[22] but not tissue inhibitors of metalloproteinase-1 and -2 levels,[23] from baseline to study end in adults with PAH; this finding also correlated with a significant ($p < 0.05$) increase from baseline to month 12 in 6-minute walk distance.[22] Because decreased MMP-2 and -9 activity leads to altered turnover and accumulation of extracellular matrix (ECM) proteins, which in turn may be associated with vascular remodeling in patients with PAH, bosentan-associated increases in MMP-9 levels may stimulate turnover of ECM proteins.[22]
- Although the pharmacokinetics of bosentan and sildenafil were altered when these two drugs were coadministered[10,12] (section 2), it appears that the acute hemodynamic effects of sildenafil may not be affected by bosentan.[24] For example, in adult patients with PAH who were already receiving maintenance dosages of bosentan, a single dose of sildenafil decreased mean pulmonary vascular resistance by 15%, which was similar to the reductions of 15–27% that have previously been observed with sildenafil monotherapy.[24] However, the manufacturer's EU prescribing information recommends that the combination be used with caution.[10,12]

2. Pharmacokinetic Profile

The pharmacokinetics of bosentan in pediatric patients with PAH (WHO functional class II or III) have been evaluated in two studies; one study (the FUTURE [pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion]-1 trial;[25] $n = 35$ evaluable patients; median age 7 years) assessed the pharmacokinetics of dispersible bosentan, and the other study (the BREATHE-3 trial;[20] $n = 18$ evaluable patients; mean age 5.7, 10.0, and 14.2 years in patients weighing 10–20, >20–40, or >40 kg, respectively) evaluated the pharmacokinetics of film-coated bosentan (see section 3 for further study design details). The primary objective of the FUTURE-1 trial was to demonstrate a similar bosentan exposure in pediatric patients receiving dispersible bosentan 4 mg/kg to that of adult patients receiving film-coated bosentan 125 mg (historical control [reported in Dingemanse and van Giersbergen[17]]).[25] The bosentan exposures would be deemed equivalent if the 90% confidence interval (CI) of the between-group difference (4 mg/kg vs historical controls) in the geometric mean ratio of the area under the plasma concentration-time curve during a dosage interval (AUC_τ) [primary endpoint] was within the predefined equivalence limits of 0.66 and 1.50.[25]

The pharmacokinetics of film-coated bosentan in healthy adults or adults with PAH have been reviewed extensively elsewhere.[13-17] This section focuses on pediatric pharmacokinetic data for dispersible bosentan 2 or 4 mg/kg twice daily[25] and film-coated bosentan 31.25, 62.5, or 125 mg twice daily (in patients weighing 10–20, >20–40, or >40 kg, respectively).[20] Pharmacokinetic data from studies in healthy adults or adults with PAH are included where pediatric data are unavailable; these supplementary data are from original research articles,[26,27] the manufacturer's prescribing information,[10,12] or European Medicines Agency (EMEA) assessment documents for bosentan.[4,28]

Data comparing the *in vivo* bioavailability of the film-coated and dispersible tablet formulations of bosentan are currently lacking.[10,28] Until such data are available, use of the dispersible tablet should be reserved for patients who are unable to take the film-coated tablet[10,28] (section 5).

Absorption and Distribution

- The absolute oral bioavailability of bosentan in healthy adults is ≈50%, and is unaffected by food.[10,12]
- In healthy adults, the pharmacokinetics of bosentan were both dose- and time-dependent, and steady-state concentrations were generally reached within 3–5 days of treatment initiation.[10,12]
- Bosentan demonstrated non-dose-proportional pharmacokinetics after multiple dosages in children, with exposure being similar in pediatric patients receiving either bosentan 2 or 4 mg/kg twice daily.[25] In addition, geometric mean maximum plasma concentration (C_{max}) [583 vs 649 ng/mL] and AUC_τ (3577 vs 3371 ng • h/mL) were similar in children receiving dispersible bosentan 2 or 4 mg/kg twice daily in the FUTURE-1 trial, suggesting that an exposure plateau is reached at a dose of 2 mg/kg in children; median time to C_{max} (t_{max}) was 3.0 hours after administration of either dosage in this study.[25]
- In children and adolescents receiving film-coated bosentan 31.25, 62.5, or 125 mg twice daily in the BREATHE-3 trial, the week-12 geometric mean C_{max} was 685, 1136, and 1200 ng/mL, respectively, and the geometric mean AUC_τ was 3496, 5428, and 6124 ng • h/mL;[20] corresponding values for median t_{max} were 2.5, 1.0, and 1.8 hours.

• Although a plateau in bosentan exposure was also observed in healthy adults (n = 24; historical control),[17] it appears to occur at a lower dose in children than in adults (2 vs ≈7 mg/kg).[25] The reason behind this is unclear, although it is possible that the exposure plateau is lower in children because of a reduced capacity to absorb bosentan, which in turn may be caused by a smaller intestinal surface area and/or different absorption characteristics relative to adults.[25]

• In pediatric patients receiving dispersible bosentan 4 mg/kg twice daily in FUTURE-1, the average steady-state exposure to bosentan was approximately half that observed in adults with PAH receiving film-coated bosentan 125 mg twice daily (n = 11; historical control), as evidenced by a geometric mean ratio of AUC_τ in children and adults of 0.54 (95% CI 0.37, 0.78); this ratio was not within the predefined limits for equivalence (0.66, 1.50).[25]

• In addition, after multiple-dose administration of film-coated bosentan 31.25, 62.5, or 125 mg twice daily, bosentan exposure was ≈25–57% lower (AUC_τ = 3496–6124 vs 8149 ng • h/mL) in children and adolescents in the BREATHE-3 trial[20] than in adults with PAH who received film-coated bosentan 125 mg twice daily in a previous study.[10,12]

• In BREATHE-3, geometric mean AUC_τ was lower after multiple doses of film-coated bosentan 31.25, 62.5, or 125 mg twice daily than after a single 31.25, 62.5, or 125 mg dose (3496–6124 vs 5453–10 777 ng • h/mL),[20] consistent with the dose-dependent auto-induction of metabolizing liver enzymes (i.e. the cytochrome P450 [CYP] 2C9 and CYP3A4 isozymes) observed in healthy adult recipients of bosentan.[20,27]

• In healthy adults, the volume of distribution of bosentan was ≈18 L after a single 250 mg intravenous dose.[10,12] However, the volume of distribution at steady state (V_{ss}) decreased with increasing dose and increased with time.[10,12] Bosentan is highly bound to plasma proteins (>98%), predominantly albumin, and does not penetrate into red blood cells.[10,12]

Metabolism and Elimination

• Bosentan is metabolized in the liver by CYP2C9 and CYP3A4 into its two main metabolites, Ro 48-5033 and Ro 47-8634, which are further metabolized to Ro 64-1056.[4] Ro 48-5033 is the only active metabolite of bosentan and may account for up to 20% of drug activity.[4] In pediatric patients receiving film-coated bosentan 31.25, 62.5, or 125 mg twice daily or dispersible bosentan 2 or 4 mg/kg twice daily, the C_{max} and AUC_τ of Ro 48-5033 was 85–93% lower than that of the parent drug; median Ro 48-5033 t_{max} was 0–5 hours.[20,25]

• After oral administration of a single dose of ^{14}C-labeled bosentan 500 mg to healthy adults, 95% of total radioactivity was excreted in the feces, mostly as Ro 48-5033; only ≈30% of fecally-excreted radioactivity was accounted for by unchanged bosentan.[26] Less than 3% of total radioactivity was excreted in the urine.[26]

• The geometric mean elimination half-life of bosentan in children and adolescents in the BREATHE-3 study was 4.7, 5.3, and 4.2 hours after a single 31.25, 62.5, or 125 mg dose of film-coated bosentan, respectively, and 6.0, 5.6, and 5.3 hours after multiple doses of bosentan 31.25, 62.5, or 125 mg twice daily.[20]

• As with V_{ss}, the systemic plasma clearance of bosentan in healthy adults decreased with increasing intravenous dose and increased with time.[10,12]

Special Populations

• Age, bodyweight, sex, WHO functional class and/or previous bosentan treatment did not appear to affect the pharmacokinetics of dispersible[25,28] or film-coated[20] bosentan in children with PAH.

• No clinically significant changes in bosentan pharmacokinetics were demonstrated in adult patients with mild hepatic impairment (Child-Pugh class A).[10,12] Although the pharmacokinetics of bosentan have not been studied in patients with moderate or severe hepatic impairment (Child-Pugh class B or C), use of this drug is contraindicated in this population because of the bosentan-associated risk of increased liver aminotransferase (i.e. ALT and AST) levels.[10,12]

• Bosentan may be used in patients with renal dysfunction, including those receiving dialysis, without the need for dosage adjustment.[10,12]

Drug Interactions

• Because bosentan is an inducer of CYP2C9, CYP3A4, and possibly CYP2C19, it is possible that plasma concentrations of drugs that are metabolized by these isozymes will be decreased when coadministered with bosentan; therefore, it may be necessary to adjust the dosage of the other agent when initiating, discontinuing, or changing the dosage of bosentan.[10,12]

• Concomitant use of bosentan with inhibitors of CYP2C9 or CYP3A4 should be approached with caution. Furthermore, coadministration of bosentan with both a potent CYP3A4 (e.g. ketoconazole, itraconazole, and ritonavir) and CYP2C9 (e.g. voriconazole) inhibitor should be avoided, because this may lead to large increases in bosentan plasma concentrations; concomitant use with fluconazole (an inhibitor of CYP2C9 and, to a lesser extent, CYP3A4) is also not recommended.[10,12]

• The plasma concentration of bosentan was decreased by 58% (and up to 90% in some patients) by concomitant use of the drug with rifampin (rifampicin) [a potent CYP2C9 and CYP3A4 inducer], and the combination is expected to result in decreased bosentan efficacy.[10,12] Coadministration of bosentan with other CYP3A4 inducers (e.g. carbamazepine, phenobarbital, and hypericum [St John's wort]) may also result in reduced bosentan exposure.

• Coadministration of bosentan and the calcineurin inhibitor cyclosporine A (ciclosporin A; a CYP3A4 substrate) resulted in an ≈30-fold increase in initial bosentan trough concentrations and a 3- to 4-fold increase in steady-state plasma concentrations relative to bosentan monotherapy.[10,12] This was thought to be a result of cyclosporine A-induced inhibition of transport protein-mediated uptake of bosentan into hepatocytes. In contrast, cyclosporine A plasma concentrations were decreased by ≈50% when coadministered with bosentan. Because of this, concomitant use of bosentan and cyclosporine A is contraindicated. For similar reasons, concomitant use of bosentan with sirolimus or tacrolimus is not recommended.[10,12]

• Plasma concentrations of bosentan and glyburide (glibenclamide; a CYP3A4 substrate) were decreased by 29% and 40% when the two drugs were coadministered, and an increased incidence of ALT and/or AST elevations was also observed; therefore, this combination should be avoided.[10,12]

• Although the use of bosentan in combination with the antiretroviral agent nevirapine has not been studied, coadministration of these agents is not recommended because nevirapine-associated hepatotoxicity may cumulate with bosentan-related liver toxicity.[10,12]

• The minimum plasma concentration of bosentan was increased and the AUC of lopinavir and ritonavir decreased when these drugs were coadministered. Therefore, the tolerability of bosentan and efficacy of ritonavir-boosted protease inhibitors, such as lopinavir plus ritonavir, should be monitored when these agents are combined.[10,12]

• Caution should be exercised when bosentan is administered in conjunction with sildenafil, as concomitant administration of these two agents resulted in a 50% increase in bosentan AUC and 63% decrease in sildenafil AUC.[10,12]

• Coadministration of bosentan and simvastatin resulted in decreased plasma simvastatin and β-hydroxy acid (active metabolite of simvastatin) concentrations by 34% and 46%; therefore, cholesterol levels should be monitored closely and simvastatin dosage adjusted as appropriate.[10,12]

• Because bosentan and epoprostenol have different metabolism and excretion profiles, concomitant use of the two drugs did not affect the pharmacokinetics of bosentan.[10,12,20,25]

• The pharmacokinetics of bosentan were not affected by coadministration with digoxin or warfarin.[10,12] In addition, bosentan did not appear to inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, or 3A4 *in vitro*; therefore, bosentan is unlikely to increase plasma concentrations of drugs metabolized by these isozymes.[10,12]

3. Therapeutic Efficacy

In Patients Receiving Dispersible Bosentan: the FUTURE-1 and -2 Trials

The efficacy of dispersible bosentan was investigated as an exploratory measure in the noncomparative, multicenter, phase III FUTURE-1 trial that was primarily designed to evaluate the pharmacokinetics of dispersible bosentan in children[25] (see section 2 for pharmacokinetic results). Preliminary efficacy results of an extension to the FUTURE-1 trial (the FUTURE-2 trial) are also available as an abstract and oral presentation.[29]

Patients aged ≥2 to <12 years with WHO functional class II or III idiopathic or heritable PAH were included in the FUTURE-1 trial if they had an arterial oxygen saturation of >88% at rest and if they were stable in terms of the disease and associated treatment; patients who had previously received bosentan or who were receiving the drug up until study commencement were also included in the trial.[25] Exclusion criteria included ALT and/or AST levels >3 × the upper limit of normal (ULN) and a bodyweight of <4 kg.

FUTURE-1 was conducted in three phases: the screening phase (4 weeks), treatment phase (12 weeks), and post-treatment follow-up phase (28 days).[25] Patients weighing <30 kg received dispersible bosentan 2 mg/kg twice daily for 4 weeks and were then up-titrated to a maintenance dosage of 4 mg/kg twice daily, which they received for the remainder of trial. The initial dosage of dispersible bosentan in patients weighing ≥30 kg was 64 mg twice daily with up-titration to 120 mg twice daily after 4 weeks. Patients already receiving bosentan at a dosage >2 mg/kg at the start of the trial were administered bosentan at the maintenance dosage for the entire study duration (at the investigator's discretion). All study medication was administered dispersed in water. Concomitant treatment with intravenous epoprostenol, inhaled or intravenous iloprost, and/or calcium channel antagonists was permitted during the course of the study.

At the completion of FUTURE-1,[25] patients were given the opportunity to participate in the FUTURE-2 study.[29] In this extension trial,[29] patients received dispersible bosentan at the maintenance dosage they were receiving at the end of FUTURE-1.

The combined study duration of FUTURE-1 and -2 was 24 months.[29]

The primary endpoint of the FUTURE-1 trial was a pharmacokinetic one (see section 2 for pharmacokinetic results). Efficacy measures explored included WHO functional class and scores for the 10-item short form survey for children (SF-10) and Clinical Global Impression (CGI) scales, as assessed by parents and the study investigator.[25] Kaplan-Meier survival estimates were calculated in the preliminary analysis of the FUTURE-2 trial; results of other efficacy measures assessed in FUTURE-2 are not yet available.[29]

A total of 36 children were enrolled in FUTURE-1 and 35 were evaluable for efficacy;[25] 3 patients did not participate in FUTURE-2.[29] Of the initial 36 patients (median age 7 years), 58% were male; 11%, 25%, and 64% were aged 2–3, 4–5, and 6–11 years, respectively; 81% weighed <30 kg; 86% had idiopathic PAH; 23 (64%) had WHO functional class II PAH, and 13 (36%) had WHO functional class III PAH; and 25% were receiving epoprostenol.[25,29]

- The dispersible tablet formulation of bosentan appeared beneficial in the treatment of pediatric patients with PAH. After 12 weeks' treatment with bosentan, WHO functional class had either improved (from class II to I [2 of 23 patients] or III to II [3 of 12]) or remained stable (at class II [20 of 23] or III [9 of 12]) in the majority of patients (figure 1); WHO functional class worsened from baseline to study end (from class II to III) in one patient.[25]
- According to parent-rated CGI scale scores at week 12 (n = 34 evaluable patients for this endpoint), PAH was 'better' or 'significantly better' in 53% (18 of 34) of pediatric patients, unchanged in 44% (15 of 34) of patients, and 'worse' or 'significantly worse' in 3% (1 of 34) of patients relative to baseline scores;[25] in the group rated as unchanged, baseline ratings for PAH were 'good' or 'very good' in 47% (7 of 15) of patients and 'bad' or 'not good or bad' in 53% (8 of 15) of patients.
- Investigator-assessed CGI scale scores indicated that disease had either stabilized or improved from baseline to week 12 in all but two (6%) patients;[25] the disease severity of the latter two patients was considered to be 'good' or 'very good' at baseline.
- There was no clinically significant improvement from baseline to week 12 in the SF-10 physical summary and psychological summary scores.[25]
- Pediatric patients who had not received bosentan prior to study commencement appeared to show greater signs of clinical improvement (assessed by any efficacy endpoint) than those who had previously received bosentan.[25] In addition, signs of clinical worsening were only seen in the group of patients who had received bosentan prior to study commencement.
- According to preliminary results of the FUTURE-2 trial, the Kaplan-Meier survival estimate at both 12 and 24 months was 91%.[29]

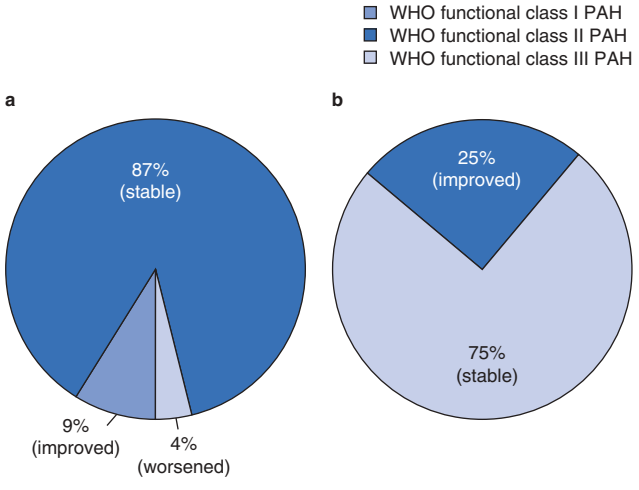

Fig. 1. Efficacy of oral dispersible bosentan in the management of children with WHO functional class II or III pulmonary arterial hypertension (PAH). Results of a noncomparative, multicenter, phase III trial (the FUTURE [pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion]-1 trial[25]) in which pediatric patients received target dosages of twice-daily dispersible bosentan 4 mg/kg (in patients weighing <30 kg) or 120 mg (in patients weighing ≥30 kg) for 12 weeks. Figures show the percentage of children with WHO functional class I, II, or III PAH at study end when stratified according to baseline WHO functional class. (**a**) Represents children with WHO functional class II PAH at baseline (n = 23) and (**b**) represents those with WHO functional class III PAH at baseline (n = 12). No statistical analyses are available for these results.

In Patients Receiving Film-Coated Bosentan

The efficacy of film-coated bosentan in pediatric patients with idiopathic or CHD-related PAH was investigated as an exploratory measure in the open-label, prospective, multicenter BREATHE-3 trial that primarily examined the pharmacokinetics of this formulation of bosentan in children and adolescents[20] (see section 2 for pharmacokinetic results). Additional efficacy data are available from an open-label, prospective, multicenter trial in adults and children with PAH associated with systemic-to-pulmonary shunt[30] and from numerous retrospective analyses in children with PAH of various causes.[31-34] Some retrospective data are available as posters and/or abstracts.[32,34]

The BREATHE-3 Study

The BREATHE-3 study enrolled pediatric patients aged 3–15 years with WHO functional class II or III PAH.[20] The study was divided into a screening period (3–21 days) followed by a 12-week treatment period. Bosentan dosage was determined by patient weight, with the target dosage of bosentan being 31.25 mg twice daily in those weighing 10–20 kg, 62.5 mg twice daily in

those weighing >20–40 mg, and 125 mg twice daily in those weighing >40 kg; all patients received bosentan at half the target dosage for the first 4 weeks of the study, except for patients weighing 10–20 kg who received bosentan at the target dose only once daily for the first 4 weeks. Coadministration of drugs that could influence bosentan pharmacokinetics (e.g. inhibitors or inducers of CYP2C9 or CYP3A4 [section 2]) was not permitted during the study period.[20]

Efficacy endpoints assessed included hemodynamic measures (i.e. cardiac index, mean pulmonary artery pressure, pulmonary vascular resistance index and systemic vascular resistance index) and WHO functional class; in patients aged ≥8 years, exercise capacity was also assessed by means of the 6-minute walk test and cardiopulmonary exercise testing with progressive cycle ergometry.[20]

A total of 19 patients were enrolled in BREATHE-3, of which 53% were female; 15 (79%) had WHO functional class II PAH and 4 (21%) had WHO functional class III PAH; 47% had PAH related to CHD (but none related to Eisenmenger's syndrome); and 53% were receiving epoprostenol.[20] The mean age of patients weighing 10–20, >20–40, or >40 kg was 5.7, 10.0, and 14.2 years, respectively.

- Bosentan was associated with significant improvements with regard to the majority of hemodynamic measures.[20] After 12 weeks of film-coated bosentan, mean pulmonary artery pressure was significantly ($p < 0.05$) reduced from 60 mmHg at baseline to 52 mmHg, mean pulmonary vascular resistance index was significantly ($p < 0.05$) reduced from 1209 to 910 dyn • sec • m^2/cm^5, and mean systemic vascular resistance index was significantly ($p < 0.05$) reduced from 1674 to 1248 dyn • sec • m^2/cm^5. The change in mean cardiac index from baseline (4.0 L/min/m^2) to study end (4.5 L/min/m^2) was not significant.
- The efficacy of film-coated bosentan did not appear to be affected by coadministration of epoprostenol.[20] For example, no significant differences in the changes in hemodynamic measures were demonstrated between the subgroup of pediatric patients who received concomitant epoprostenol during the study (n = 10) and those patients who did not (n = 9). In addition, hemodynamic measures in patients who did or did not receive concomitant epoprostenol were not dissimilar to those in the combined study population.
- After 12 weeks' treatment with film-coated bosentan, WHO functional PAH class had either improved (from class II to I [2 of 15] or III to II [3 of 4]) or remained stable (at class II [12 of 15] or III [1 of 4]) in the majority of pediatric patients; only one child had PAH that had deteriorated over the course of the study (from class II to III).[20]
- There was no significant difference from baseline to week 12 in the exercise capacity of pediatric patients aged ≥8 years (n = 12) in terms of peak oxygen consumption (mean change = 53 mL/min) or mean walk distance (492 m at baseline and week 12).[20]

Other Studies

Where specified, pediatric patients in these studies who weighed <10, 10–20, 20–40, or >40 kg received film-coated bosentan ≈15,[31,33] 31.25,[30,31,33] 62.5,[30,31,33] or 125[30,31,33] mg twice daily, respectively.

- In ten children and adolescents (aged 5–17 years) with WHO functional class III or IV CHD-related PAH (including patients with Eisenmenger's syndrome) who participated in a prospective, cohort trial,[30] treatment with bosentan (median of 2.4 years) was associated with significant improvements from baseline to 4-month, 1-year, and 1.5-year follow-up in WHO functional class (all $p = 0.03$), and from baseline to 4-month follow-up in mean walk distance ($p = 0.04$; assessed by the 6-minute walk test). However, after a median follow-up of 2.7 years, the difference in these efficacy measures from baseline was no longer significant, and walk distances appeared to have declined by a mean of ≈46 m from baseline (value estimated from a graph).[30]
- According to prespecified criteria, persistence of the beneficial effect of bosentan was 80% at both 1 and 2 years in this prospective, cohort study.[30] However, the estimate was lower when the decline in mean walk distance and addition of PAH-specific therapies (e.g. a prostanoid and/or sildenafil) was taken into account (50% at 1 year and 20% at 2 years).
- In retrospective analyses of 86,[31] 40,[33] and 15[34] pediatric patients (aged 5 months to 21 years) with PAH of New York Heart Association class III or IV[34] or WHO functional class II–IV[33] or I–IV,[31] treatment with film-coated bosentan (with or without other PAH-specific therapies) for a mean or median duration of ≈13–14 months (where specified[31,33]) was associated with stabilization of, or improvements in, WHO functional class,[31,33,34] hemodynamic parameters,[31,34] walk distance,[33] and/or patient bodyweight.[33]
- In two of the retrospective studies,[31,34] WHO functional class was either stable (in 34 of 78 [44%] evaluable patients[31]) or had improved by at least one class from baseline to study end (in 36 of 78 [46%][31] or 13 of 15 [87%][34] patients) in the majority of pediatric patients. In the other study,[33] WHO functional class was improved significantly ($p = 0.001$) from baseline to study end in pediatric patients with PAH associated with various underlying disorders (n = 20), but the difference did not reach significance in those with idiopathic PAH (n = 20).

- Significant reductions from baseline in mean pulmonary artery pressure ($p = 0.005$) and pulmonary vascular resistance ($p = 0.01$) were demonstrated in one retrospective analysis,[31] and median right ventricular systolic pressure decreased from 69 mmHg at baseline to 60 mmHg at study end in another.[34] In addition, arterial oxygen saturation and proBNP levels appeared to have improved from baseline to study end in the latter trial,[34] although statistical analyses are not available.
- In one retrospective analysis,[33] mean walk distance improved significantly ($p = 0.002$) from baseline to study end in patients aged ≥5.5 years with other disorders associated with PAH ($n = 11$) receiving film-coated bosentan, but this difference was not significant in those with idiopathic PAH ($n = 10$). In children aged <5.5 years ($n = 19$), patient weight was improved to a significant extent ($p = 0.01$) from baseline to study end regardless of PAH type;[33] in this analysis, patient weight was used to assess clinical response in children who were too young to perform a 6-minute walk test.[33]
- The Kaplan-Meier estimate of disease progression was 56% at year 3 and 67% at year 4, and survival estimates at years 1–4 were 86–98%, in pediatric patients participating in one retrospective trial[31] who were followed up for an extended, median duration of 30 months after a median exposure to film-coated bosentan of 24 months.[32]

4. Tolerability

Short-term tolerability data for oral bosentan in pediatric patients with PAH are available from two 12-week studies (FUTURE-1[25] and BREATHE-3[20]) discussed in sections 2 and 3. Cumulative tolerability data from the short-term FUTURE-1 trial and preliminary results of a longer-term extension phase of this trial (FUTURE-2; median exposure to bosentan 25 months) are available as an abstract and oral presentation.[29] Additional tolerability data from these studies are available from an EMEA assessment document.[28] Data from previous reviews,[13,14,16] the manufacturer's prescribing information,[10,12] and a prospective, internet-based postmarketing study (Actelion TRAX [TRAcleer eXcellence postmarketing surveillance program]) for film-coated bosentan are also discussed where appropriate.[35]

- Long- or short-term bosentan was generally well tolerated in pediatric patients with PAH, regardless of the formulation administered.[20,25,29] In clinical trials, most adverse events were mild or moderate in severity[28] and, where specified, resolved with continued treatment.[25]
- The tolerability profile of bosentan in pediatric patients was not dissimilar to that already observed in adults with regard to the nature of specific adverse events.[20,25]
- In FUTURE-1, at least one adverse event was reported in 22 of 36 pediatric patients (61%) receiving dispersible bosentan 2 or 4 mg/kg twice daily. Abdominal pain (4 of 36 patients [11%]), vomiting (3 of 36 patients [8%]), aggression, asthenia, bronchitis, chest pain, extremity pain, fatigue, flushing, headache, nasal congestion, pulmonary hypertension, tonsillitis, upper abdominal pain, and viral infection (2 of 36 patients [6%] for each) were the most frequently occurring adverse events observed in FUTURE-1.[25]
- After a median duration of 25 months' treatment with dispersible bosentan 2 or 4 mg/kg twice daily, at least one adverse event was reported in 81% (29 of 36) of pediatric patients according to cumulative results of the FUTURE-1 and -2 trials.[29] Infections (53% [19 of 36]), respiratory or thoracic disorders (39% [14 of 36]), and gastrointestinal disorders (36% [13 of 36]) were the most frequently reported adverse events in these trials.[29]
- In BREATHE-3, the most commonly reported adverse events in pediatric patients receiving film-coated bosentan 31.25–125 mg twice daily were flushing (4 of 19 patients [21%]), edema, and headache (3 of 19 patients [16%] for each).[20]
- Changes in vital signs, bodyweight, or ECG parameters were not observed in the FUTURE-1 trial.[25] Although small decreases from baseline in mean standing systolic (–2 mmHg) or diastolic (–6 mmHg) blood pressure were reported at week 12 in the BREATHE-3 trial, these appeared to resolve over the course of the study and did not result in symptomatic hypotension;[20] no changes in heart rate or ECG parameters were observed.
- Serious adverse events occurred in 11% (4 of 36) of pediatric patients in the FUTURE-1 trial; only one episode (worsening of PAH) was thought to be treatment-related.[25] During FUTURE-1 and -2, at least one serious adverse event occurred in 42% (15 of 36) of patients; respiratory or thoracic disorders (8 of 36 [22%]), infections (6 of 36 [17%]), and surgical or medical procedures (4 of 36 [11%]) were the most frequently occurring serious adverse events associated with longer term bosentan, followed by cardiac, general, and nervous system disorders (3 of 36 [8%] each).[29] Two patients died of worsening PAH during the FUTURE-2 study, giving a total of three deaths for FUTURE-1 and -2 combined.[29]
- In the BREATHE-3 trial, serious adverse events included dizziness, hypertension, tachycardia, and tremor in one child, and increased ALT levels in another child; the episode of increased ALT levels was likely caused by ulcerative colitis-associated sclerosing cholangitis and resolved after discontinuation of bosentan.[20] There were no treatment-related deaths during the trial.[20,25]

• Two study discontinuations occurred in FUTURE-1, with one resulting from patient death and the other from dislike of the taste of the medication; the patient death was caused by right heart failure following an ear infection and was not thought to be treatment-related.[25] Study discontinuations due to nonfatal bosentan-associated adverse events (PAH worsening, increased dyspnea on exertion, treatment failure, and autoimmune hepatitis) occurred in four patients (11%) during FUTURE-1 or -2.[29] In BREATHE-3, one patient with a low bodyweight discontinued bosentan because of adverse events.[20]

• Bosentan has been associated with dose-dependent increases in ALT and AST levels to >3 × ULN in 11–14%, and >8 × ULN in 2–7%, of adults receiving oral bosentan 125 or 250 mg twice daily in clinical trials;[13,14,16] these elevations all resolved spontaneously or upon cessation of bosentan or reduction of dosage. In the pediatric studies discussed in this section, ALT and/or AST levels were increased in 3% (1 of 36) of pediatric patients receiving dispersible bosentan for a median duration of 25 months in the FUTURE-2 trial (increased to >3 × ULN),[29] and in 16% (3 of 19) of those receiving film-coated bosentan for 12 weeks in the BREATHE-3 trial;[20] no episodes of liver enzyme elevation occurred during the FUTURE-1 trial.[25]

• ALT and AST elevations typically occur within the first 26 weeks of treatment and are possibly due, at least in part, to competitive inhibition of the elimination of bile salts from hepatocytes, although other mechanisms may also be involved.[10,12] Because of this, bosentan is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh class B or C) or baseline ALT and/or AST levels >3 × ULN. It is also recommended that AST and ALT levels are assessed before and during treatment with bosentan[10,12] (section 5).

• Bosentan has also been associated with dose-related decreases in hemoglobin levels.[13,14,16] In adults, clinically significant decreases in hemoglobin levels occurred in 3–6% of bosentan recipients in clinical trials;[13,14,16] in the pediatric studies discussed in this section, no episodes of anemia were reported.[20,25,29] Hemoglobin decreases are not progressive and usually stabilize within 4–12 weeks of bosentan commencement;[10,12] levels should be checked before and during treatment (section 5).

• No abnormalities in laboratory parameters other than ALT and AST elevations were observed during the BREATHE-3 trial.[20]

Postmarketing Experience

• In the Actelion TRAX postmarketing study, which included 146 patients aged 2–11 years (median exposure to bosentan ≈29 weeks) and 4443 patients aged ≥12 years (median exposure to bosentan ≈30 weeks), it appeared that bosentan was tolerated better by children than by adolescents and adults, although statistical analyses were not performed for any of the comparisons.[35] For example, 4 of 146 (3%) pediatric patients and 345 of 4443 (8%) adolescent or adult patients had increases in ALT and/or AST levels; these elevations were all ≤5 × ULN in children, whereas 17% (57 of 345) and 18% (62 of 345) of ALT and/or AST elevations were >5 to ≤8 or >8 × ULN in adolescents or adults.[35]

• In addition, 14% of children and 28% of adolescents or adults discontinued bosentan treatment, and 3% and 4% discontinued treatment because of an adverse event.[35] In the pediatric group, the adverse event-related treatment discontinuations were caused by aggravated cardiac failure, worsening of PAH, or cardiomyopathy/intracardiac thrombus/cardiac failure/worsening of PAH; a fourth was of unknown nature. In both children and adolescents/adults, death (8% vs 9%) and hospitalization (4% vs 4%) were the most common causes of treatment discontinuation.

5. Dosage and Administration

In the EU, oral dispersible[10] and film-coated[12] bosentan tablets are approved to improve exercise capacity and symptoms in patients with WHO functional class III PAH, including those with idiopathic or heritable PAH, PAH secondary to scleroderma (without significant interstitial pulmonary disease), or PAH associated with CHD (e.g. systemic-to-pulmonary shunt or Eisenmenger's physiology); benefits have also been seen in patients with WHO functional class II PAH. Because the *in vivo* bioavailability of these two formulations has not yet been compared, the dispersible formulation should be reserved for use in patients who are unable to take the film-coated tablets.[10,28]

The optimal maintenance dosage of bosentan in pediatric patients aged ≥2 years has not been clearly defined in well controlled studies.[10,12] However, bosentan dosages of 2–4 mg/kg twice daily were beneficial in pediatric patients in clinical studies (section 3). Although formal studies comparing the efficacy and safety of bosentan 2 mg/kg twice daily with that of 4 mg/kg twice daily have not been performed, based on results of a pharmacokinetic study (section 2), the higher dosage of bosentan is expected to be no more effective in children than the lower dosage.[10,12] Bosentan may be administered in the morning and evening, without regard to food.[10,12]

Because bosentan was associated with elevations in ALT and/or AST levels in clinical trials and a postmarketing surveillance study (section 4), ALT and AST levels must be measured prior to commencement of bosentan treatment, every month for the duration of treatment, and 2 weeks after an increase in bosentan dosage (please see local prescribing information for further details regarding dosage adjustments and monitoring requirements).[10,12] If

clinical symptoms of liver injury occur (e.g. abdominal pain, jaundice, flu-like syndrome, fever, or vomiting), bosentan should be discontinued and not re-introduced.[10,12] Hemoglobin levels should also be assessed prior to the commencement of bosentan therapy, monthly for the first 4 months of treatment, and every 3 months thereafter.[10,12]

Bosentan is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B or C) or baseline ALT or AST levels >3 × ULN, and in those receiving cyclosporine A;[10,12] no dosage adjustment is necessary for those with mild hepatic impairment (Child-Pugh class A). Adults with a systolic BP ≤85 mmHg should not receive bosentan;[10,12] no specific BP parameters are described for children. In addition, administration of bosentan with fluconazole, glyburide, nevirapine, sirolimus, or tacrolimus is not recommended (section 2); coadministration with both a CYP2C9 and CYP3A4 inhibitor is also not recommended.[10,12] No dosage adjustments on the basis of renal impairment are required.[10,12]

Local manufacturer's prescribing information should be consulted for comprehensive information on dosage and administration, contraindications, precautions and warnings, drug interactions, recommendations in cases of ALT and/or AST elevations, and patient monitoring requirements.

6. Bosentan: Current Status in Pediatric Patients with Pulmonary Arterial Hypertension

In the EU, oral bosentan is approved to improve exercise capacity and symptoms in patients with PAH of WHO functional class III; benefits have also been seen in patients with WHO functional class II PAH. Bosentan is available as film-coated tablets, and a new dispersible formulation of bosentan has also recently been approved in the EU for the treatment of PAH in children aged ≥2 years.

A noncomparative, multicenter, phase III trial (FUTURE-1) that was primarily designed to investigate the pharmacokinetics of dispersible bosentan in pediatric patients, demonstrated that increasing the dosage of bosentan from 2 to 4 mg/kg twice daily was unlikely to result in increased exposure to bosentan. In addition, exploratory measures of efficacy in this trial demonstrated that target dosages of twice-daily dispersible bosentan 4 mg/kg (in patients weighing <30 kg) or 120 mg (in patients weighing ≥30 kg) for 12 weeks were beneficial in pediatric patients (aged ≥2 to <12 years) with WHO functional class II or III PAH. In another study of similar design (BREATHE-3), film-coated bosentan administered as a weight-adjusted target dose of 31.25–125 mg twice daily for 12 weeks was associated with significant improvements in hemodynamic measures in a similar population of patients aged 3–15 years. Bosentan was generally well tolerated.

Acknowledgments and Disclosures

This manuscript was reviewed by: ***S.A. Antoniu***, Department of Internal Medicine II-Pulmonary Disease, University of Medicine and Pharmacy "Gr.T.Popa" Iasi, Iasi, Romania; ***M. Beghetti***, Pediatric Cardiology Unit, Children's University Hospital, Geneva, Switzerland; ***K.K. Talwar***, Department of Cardiology, Postgraduate Institute of Medical Education & Research, Chandigarh, India.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2009 Oct; 30 (20): 2493-537
2. van Albada ME, Loot FG, Fokkema R, et al. Biological serum markers in the management of pediatric pulmonary arterial hypertension. Pediatr Res 2008 Mar; 63 (3): 321-7
3. Rosenzweig EB, Barst RJ. Pulmonary arterial hypertension: a comprehensive review of pharmacological treatment. Treat Respir Med 2006; 5 (2): 117-27
4. European Medicines Agency. Tracleer® (bosentan) scientific discussion [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tracleer/100002en6.pdf [Accessed 2009 Oct 13]
5. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension: results from a National Prospective Registry. Ann Intern Med 1991 Sep; 115 (5): 343-9
6. Widlitz A, Barst RJ. Pulmonary arterial hypertension in children. Eur Respir J 2003; 21: 155-76
7. Haworth SG, Hislop AA. Treatment and survival in children with pulmonary arterial hypertension: the UK Pulmonary Hypertension Service for Children 2001-2006. Heart 2009 Feb; 95 (4): 312-7
8. Haworth SG. The management of pulmonary hypertension in children. Arch Dis Child 2008; 93 (7): 620-5
9. Actelion Ltd. Tracleer (bosentan) receives EU approval for pediatric formulation - the first and only licensed pulmonary arterial hypertension therapy for children [online]. Available from URL: http://www.actelion.com/en/our-company/news-and-events/index.page?newsId=1327164 [Accessed 2009 Sep 15]
10. Actelion Pharmaceuticals Ltd. Tracleer® 32 mg dispersible tablets: EU prescribing information [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tracleer/emea-combined-h401en.pdf [Accessed 2009 Nov 25]
11. Price LC, Howard LSGE. Endothelin receptor antagonists for pulmonary arterial hypertension: rationale and place in therapy. Am J Cardiovasc Drugs 2008; 8 (3): 171-85
12. Actelion Pharmaceuticals Ltd. Tracleer® 62.5 and 125 mg film-coated tablets: EU prescribing information [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tracleer/emea-combined-h401en.pdf [Accessed 2009 Nov 25]
13. Dhillon S, Keating GM. Bosentan: a review of its use in the management of mildly symptomatic pulmonary arterial hypertension. Am J Cardiovasc Drugs 2009; 9 (5): 331-50
14. Oldfield V, Lyseng-Williamson KA. Bosentan: a review of its use in pulmonary arterial hypertension and systemic sclerosis. Am J Cardiovasc Drugs 2006; 6 (3): 189-208
15. Prakash A, Perry CM. Bosentan. Am J Cardiovasc Drugs 2002; 2 (5): 335-42
16. Dhillon S. Bosentan: a review of its use in the management of digital ulcers associated with systemic sclerosis. Drugs 2009; 69 (14): 2005-24

17. Dingemanse J, van Giersbergen PLM. Clinical pharmacology of bosentan, a dual endothelin receptor antagonist. Clin Pharmacokinet 2004; 43 (15): 1089-115
18. Clozel M, Breu V, Gray GA, et al. Pharmacological characterization of bosentan, a new potent orally active nonpeptide endothelin receptor antagonist. J Pharmacol Exp Ther 1994; 270 (1): 228-35
19. Hiramoto Y, Shioyama W, Kuroda T, et al. Effect of bosentan on plasma endothelin-1 concentration in patients with pulmonary arterial hypertension. Circ J 2007; 71 (3): 367-9
20. Barst RJ, Ivy D, Dingemanse J, et al. Pharmacokinetics, safety, and efficacy of bosentan in pediatric patients with pulmonary arterial hypertension. Clin Pharmacol Ther 2003 Apr; 73 (4): 372-82
21. Sfikakis PP, Papamichael C, Stamatelopoulos KS, et al. Improvement of vascular endothelial function using the oral endothelin receptor antagonist bosentan in patients with systemic sclerosis. Arthritis Rheum 2007 Jun; 56 (6): 1985-93
22. Giannelli G, Iannone F, Marinosci F, et al. The effect of bosentan on matrix metalloproteinase-9 levels in patients with systemic sclerosis-induced pulmonary hypertension. Curr Med Res Opin 2005; 21 (3): 327-32
23. Giannelli G, Iannone F, Marinosci F, et al. Clinical outcomes of bosentan in pulmonary arterial hypertension do not correlate with levels of TIMPs. Eur J Clin Invest 2006; 36 Suppl. 3: 73-7
24. Gruenig E, Michelakis E, Vachiery J-L. Acute hemodynamic effects of single-dose sildenafil when added to established bosentan therapy in patients with pulmonary arterial hypertension: results of the COMPASS-1 study. J Clin Pharmacol 2009 Nov; 49 (11): 1343-52
25. Beghetti M, Haworth SG, Bonnet D, et al. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study. Br J Clin Pharmacol 2009; 68 (6): 948-55
26. Weber C, Gasser R, Hopfgartner G, et al. Absorption, excretion, and metabolism of the endothelin receptor antagonist bosentan in healthy male subjects. Drug Metab Dispos 1999; 27 (7): 810-5
27. Weber C, Schmitt R, Birnboeck H, et al. Multiple-dose pharmacokinetics, safety, and tolerability of bosentan, an endothelin receptor antagonist, in healthy male volunteers. J Clin Pharmacol 1999; 39: 703-14
28. European Medicines Agency. EMEA assessment report for Tracleer® (EMEA/CHMP/345963/2009) [online]. Available from URL: http://www.emea.europa.eu/humandocs/PDFs/EPAR/tracleer/tracleer-H-401-X-39-AR.pdf [Accessed 2009 Nov 25]
29. Beghetti M, Berger RMF, Barst RJ, et al. Longer-term survival in paediatric patients with idiopathic or familial pulmonary arterial hypertension (IPAH/FPAH) treated with bosentan: data from the FUTURE-1 and FUTURE-2 studies [abstract no. 5176 plus oral presentation]. European Society of Cardiology Congress; 2009 Aug 29-Sep 2; Barcelona
30. van Loon RLE, Hoendermis ES, Duffels MGJ, et al. Long-term effect of bosentan in adults versus children with pulmonary arterial hypertension associated with systemic-to-pulmonary shunt: does the beneficial effect persist? Am Heart J 2007 Oct; 154 (4): 776-82
31. Rosenzweig EB, Ivy DD, Widlitz A, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension. J Am Coll Cardiol 2005 Aug; 46 (4): 697-704
32. Ivy DD, Barst RJ, Doran AK, et al. Effects of long-term bosentan in children with pulmonary arterial hypertension [abstract no. PW3-6]. Cardiol Young 2008; 18 Suppl. 1: 34. Plus poster presented at the 43rd Meeting of the Association for European Paediatric Cardiology and the 18th Spring Meeting of the European Congenital Heart Surgeons Association; 2008 May 21-24; Venice
33. Maiya S, Hislop AA, Flynn Y, et al. Response to bosentan in children with pulmonary hypertension. Heart 2006 May; 92 (5): 664-70
34. Gonçalves MR, Freitas I, Paramés F, et al. Bosentan for the treatment of pulmonary arterial hypertension in children [abstract no. P-76]. Cardiol Young 2008; 18 Suppl. 1: 67
35. Beghetti M, Hoeper MM, Kiely DG, et al. Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: results from the European Postmarketing Surveillance Program. Pediatr Res 2008 Aug; 64 (2): 200-4

Correspondence: *Natalie J. Carter*, Adis, a Wolters Kluwer Business, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand.
E-mail: demail@adis.co.nz