Safety and tolerability of bosentan in the management of pulmonary arterial hypertension

Kari E Roberts
Ioana R Preston
Pulmonary, Critical Care and Sleep Medicine, Tufts Medical Center, Boston, Massachusetts, USA

Abstract: Endothelin receptor antagonism has emerged as an important therapeutic approach in pulmonary arterial hypertension (PAH). Bench to bedside scientific research has clearly shown that endothelin-1 (ET-1) is over-expressed in several forms of pulmonary vascular disease and plays an important pathogenetic role in the development and progression of PAH. Oral endothelin receptor antagonists (ERAs) have been shown to improve exercise capacity, functional status, pulmonary hemodynamics, and delay the time to clinical worsening in several randomized placebo-controlled trials. Bosentan, the first oral ERA, was approved in 2001 and since that time it has established a strong record of safety and efficacy in PAH. More recently, two additional ERAs, ambrisentan and sitaxsentan, have been approved for use. The objective of this review is to evaluate the available evidence supporting the efficacy, pharmacology, safety and tolerability, and patient-focused perspectives for bosentan, the first approved ERA for PAH. Ongoing and forthcoming randomized trials are also highlighted including the application of bosentan in combination with other PAH therapies.

Keywords: bosentan, endothelin receptor antagonists, pulmonary arterial hypertension

Introduction
Pulmonary arterial hypertension (PAH) is a progressive arteriopathy characterized by vasoconstriction, pulmonary vascular remodeling, and in situ thrombosis. Until the mid-1980s, the prognosis for individuals diagnosed with PAH was dismal with a median survival of less than 3 years from the time of diagnosis.1 The introduction of therapies targeting the dysregulated pulmonary vasculature, including parenteral, inhaled and oral medications, has dramatically improved PAH survival. Since the discovery of ET-1 in the late 1980s, scientific research has established that excess synthesis of ET-1 is an important factor in the pathogenesis of PAH.2 A potent vasoconstrictor and mitogen, endothelin-1 (ET-1) plays a central role in the highly regulated cross-talk between the vascular smooth muscle and endothelium. This led to the development of a class of drugs called endothelin receptor antagonists (ERAs). In 1994 Clozel and colleagues reported the discovery of a dual endothelial receptor antagonist.3 Bosentan (Tracleer®; Actelion Pharmaceuticals Ltd, Allschwil, Switzerland) was approved for use in 2001, making it the first FDA-approved oral therapy for PAH.

On the basis of a series of randomized controlled clinical trials, bosentan, ambrisentan, and sitaxsentan are the ERAs licensed in the United States and/or Europe as monotherapy for patients with Group 1 World Health Organization pulmonary arterial hypertension (Table 1). This class of drug offers not only improved symptom control, but also the prospect of improved quality of life. In this review we aim to discuss the pharmacology, therapeutic benefits and safety profile of bosentan in patients with PAH. Bosentan is the first ERA to be approved for the treatment of PAH patients who are...
ET receptors are abundant on vascular smooth muscle, proliferative components of PAH pathogenesis. Its integral potential node of control in both the vasoconstrictive and cells, fibroblasts, and pericytes. This property makes it a growth and apoptosis of endothelial cells, smooth muscle. Dysregulation of ET-1 signaling can mediate to abnormal and mitogenesis via endocrine and paracrine mechanisms.

Vasomotor activity, regulates extracellular matrix formation and mitogenesis via endocrine and paracrine mechanisms. ET-1 over-expression in the plasma and the lungs of patients with PAH provided evidence that it was important in the pathogenesis of human pulmonary hypertension. More recent data have demonstrated that ET-1, in addition to its potent vasomotor activity, regulates extracellular matrix formation and mitogenesis via endocrine and paracrine mechanisms. Dysregulation of ET-1 signaling can mediate to abnormal growth and apoptosis of endothelial cells, smooth muscle cells, fibroblasts, and pericytes. This property makes it a potential node of control in both the vasoconstrictive and proliferative components of PAH pathogenesis. Its integral role in these processes made ET-1 signaling a therapeutic target for PAH.

**ET-1 receptor biology**

ET-1 acts on two G protein-coupled receptors referred to as the endothelin A (ET_	ext{A}) and endothelin B (ET_	ext{B}) receptors. ET_	ext{A} receptors are abundant on vascular smooth muscle, pericytes, and fibroblasts. Their activation by ET-1 results in vasoconstriction and proliferation in vitro. ET_	ext{B} receptors are abundant on both endothelial cells and vascular smooth muscle, particularly in the distal lung microvasculature. When bound by ET-1 ligand, ET_	ext{B} receptor response is varied, depending upon the cell type on which the receptor is expressed. In the presence of ET-1, endothelial ET_	ext{B} trigger the release of vasodilators and antiproliferative molecules such as prostacyclin and nitric oxide. In addition, endothelial ET_	ext{B} clears ET-1 from the circulation. However, when expressed on vascular smooth muscle cells, ET_	ext{B} receptors mediate ET-1 induced vasoconstriction and are pro-proliferative, much like the ET_	ext{A} receptor.

**Pharmacology and pharmacokinetics of bosentan**

ERAs are orally administered direct inhibitors of ET-1 receptors. Bosentan acts nonselectively on both the ET_	ext{A} and ET_	ext{B} receptors (ET_	ext{A}: ET_	ext{B} 20:1), whereas both sitaxsentan (ET_	ext{A}: ET_	ext{B} 6500:1) and ambrisentan (ET_	ext{A}: ET_	ext{B} 260:1) are significantly more selective for the ET_	ext{A} receptor. Bosentan’s pharmacokinetics are dose-proportional up to 600 mg (single dose) and 500 mg (multiple doses) daily. It is dosed 62.5 mg twice a day the first 4 weeks and 125 mg twice a day thereafter. No dose adjustment is required in adults based on sex, age, bodyweight or mild hepatic impairment. Following oral administration, bosentan reaches peak plasma concentrations after about 3 hours, and it reaches steady state conditions after 3 to 5 days.

Bosentan’s bioavailability is about 50%, and is similar for either a single 125 mg tablet or two 62.5 mg tablets. Concomitant intake of food does not have a significant impact on absorption.

**Distribution, metabolism and elimination**

Bosentan is highly protein-bound, with approximately 98% bound to albumin. It is metabolized by the hepatic cytochrome P450 (CYP) enzymes CYP3A4 and CYP2C9. Three metabolites are formed, one of which, Ro 48–5033, is biologically active, and may contribute to up to 20% of the parent compound’s action. The elimination of unchanged bosentan and its metabolites is primarily through the biliary system, with less than 3% excreted renally. The half-life of bosentan is 5 to 8 hours. Due to its interaction with the cytochrome P450 enzymes, bosentan should be avoided in patients with moderate to severe liver disease or baseline liver transaminases greater than 3 times the upper limit of normal (see Safety and tolerability).
Drug interactions

Bosentan induces members of the cytochrome P450 family. Administration of bosentan therefore leads to increased metabolism of warfarin, and cyclosporin A, and HMG CoA reductase inhibitors. Combined use of these medications must be carefully considered, as clearance can be increased by up to 50%, necessitating dose adjustments in order to maintain therapeutic efficacy. Concomitant administration of bosentan and inhibitors of CYP3A4, such as the azole fungicides, can increase the peak plasma concentration of bosentan by more than 2-fold. Lastly, use of bosentan and the oral hypoglycemic glyburide is contraindicated due a higher incidence of hepatotoxicity and reduced plasma levels of both drugs.

Two additional interactions deserve special attention in the PAH patient. First is the interaction with phosphodiesterase 5 (PDE5) inhibitors. Treatment with bosentan 62.5 mg twice daily was associated with a two-fold increase in sildenafil clearance. Increasing the dose of bosentan to 125 mg twice daily led to a further increase in sildenafil oral clearance, demonstrating that bosentan, in a dose dependent manner, decreases the plasma concentration of sildenafil by as much as 55%.

Similarly, in healthy volunteers, bosentan decreased tadalafil exposure by 41.5%. In addition, sildenafil significantly increases bosentan plasma levels. The clinical implication of these pharmacologic interactions remains to be documented.

Second, bosentan decreases the effectiveness of hormonal oral contraceptives. Awareness of this effect is crucial for PAH patients, in whom pregnancy can induce a life-threatening pulmonary hypertensive crisis. Women of child-bearing age who are treated with bosentan must use two methods of contraception.

Practitioners prescribing bosentan must be aware of these potential drug-drug interactions, and make appropriate decisions regarding coadministration.

Safety and tolerability

Bosentan is very well tolerated. The most common adverse effect is hepatotoxicity which results from the inhibition of a bile acid export pump by bosentan and its metabolites. Elevation of liver function tests (aspartate aminotransferase – AST, alanine aminotransferase – ALT, and bilirubin) to greater than 3 times the upper limit of normal (ULN) can be seen in up to 10% of patients. Fortunately this effect is usually reversible and often improves with dose reduction, or discontinuation of therapy. In a post-market analysis of 4994 patients on bosentan followed up prospectively for 30 months, the incidence of liver function tests above 3 times ULN was 7.6%, with an annual rate of 10.1% and a discontinuation rate of 3.7%. As a result of the potential for liver toxicity, patients must have liver function assessed prior to starting bosentan, and monthly thereafter. In the event of AST and/or ALT elevations to between 3 and 5 times ULN, dose reduction should be strongly considered. More severe elevations demand dose reduction, if not interruption/cessation of bosentan, especially when associated with elevations of bilirubin, or with symptoms such as right upper quadrant pain. Initiation of bosentan therapy is not recommended for individuals with baseline liver function tests greater than 3 times ULN. It is of note that, despite the potential for hepatotoxicity, bosentan has been used without major side effects in carefully selected patients with portopulmonary hypertension in the setting of mild hepatic failure.

Other reported side effects are mild and include: leg edema (in up to 3%), mild decreases in hemoglobin, and nasal congestion. Fluid retention, typically reported as increased lower extremity edema and/or weight gain, can be seen in a minority of patients. In individuals with baseline fluid retention and/or impaired left ventricular function, this side effect has the potential to be more clinically significant, thus consideration of alternative pulmonary hypertension therapies is reasonable for these patients. Hemoglobin reductions are

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<th>Class</th>
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<tr>
<td>I</td>
<td>No significant limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope (asymptomatic)</td>
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<tr>
<td>II</td>
<td>Moderate limitation of physical activity; no discomfort at rest, but normal physical activity causes mild symptoms (dyspnea, fatigue, chest pain, or presyncope)</td>
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<tr>
<td>III</td>
<td>Marked limitation of physical activity; no discomfort at rest, but less than ordinary activity causes symptoms (dyspnea, fatigue, chest pain, or presyncope)</td>
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<tr>
<td>IV</td>
<td>Dyspnea and/or fatigue at rest, symptoms are increased by almost any physical activity; inability to perform any physical activity; signs of right heart failure may be present</td>
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generally mild (mean reduction 0.9 gm/dL), more common at higher doses, and stabilize after 12 weeks. Hemoglobin should be assessed prior to initiation, monthly for the first 12 weeks and quarterly thereafter.

**Clinical experience with bosentan in PAH**

Following favorable studies of safety and efficacy in animal models of pulmonary hypertension, the first pilot study of bosentan in humans was published in 2000. This study was designed to evaluate the dosing and safety of bosentan for patients with NYHA functional Class II, III, and IV PAH in two phases. The first phase explored the safety, efficacy and pharmacokinetics of parenteral bosentan in 7 patients. This study showed that an infusion of high doses of intravenous bosentan (50–300 mg) acutely lowered both pulmonary and systemic vascular resistance. Following drug administration there was a transient increase in ET-1 levels, consistent with the blockade of peptide clearance by endothelial ETₐ receptors. The second phase was designed to assess the functional and hemodynamic impact of oral bosentan (1000 mg twice daily) for 8 weeks. Unfortunately several of the patients died or suffered clinical deterioration during the second phase of the study necessitating early study termination.

In light of the promising hemodynamic findings, these data led to the first randomized, double-blind, placebo-controlled trial to evaluate the clinical effects of bosentan as a long-term oral treatment for idiopathic PAH or PAH related to scleroderma. All patients were NYHA Class III at baseline, and the bosentan and placebo groups were well matched at baseline, with the exception of a slightly longer duration of disease before diagnosis in the placebo group. Over 12 weeks, oral bosentan (62.5 mg twice a day for 4 weeks, then 125 mg twice daily) improved placebo-adjusted exercise capacity (6-minute walk distance, +76 meters; 95% CI 12 to 39, p = 0.21), pulmonary vascular resistance (−415 dyn s cm⁻⁵, 95% CI −608 to −221, p < 0.001), and NYHA Class. The incidence of hepatotoxicity (defined as an increase in liver function tests over 3 times upper limit of normal) in bosentan treated patients was 10% and resolved with discontinuation of the drug.

A second randomized trial designed as a 16-week, double-blind, placebo-controlled study, the Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1), showed that PAH patients treated with oral bosentan (62.5 mg twice a day for 4 weeks, then either 125 mg or 250 mg twice daily) had improved exercise capacity as measured by the 6-minute walk distance, and functional class. In addition it delayed time to clinical worsening compared to placebo. Most patients were in NYHA Class III, with a few Class IV. In both groups, more patients had idiopathic PAH than PAH associated with connective tissue disorders. Subgroup analysis revealed that bosentan improved the walking distance from baseline in patients with idiopathic PAH (46-meter increase as opposed to a 5-meter decline in the placebo group) while bosentan only prevented deterioration in the walking distance among patients with PAH related to scleroderma. Abnormal hepatic function was found to be dose dependent. Increases of hepatic transaminases to more than 8 times the upper limit of normal was seen only in the bosentan groups: 3% in the group receiving 125 mg twice daily and 7% in the group receiving 250 mg twice daily. A substudy subsequently showed that bosentan improved right ventricular size and systolic function as well as left ventricular filling according to echocardiography. BREATHE-1 resulted in approval for the first oral therapy for PAH.

A 1-year follow up, open label study evaluated the durability of clinical improvement in patients that were NYHA Class III at baseline. Six-minute walk distances, pulmonary hemodynamics and functional status were sustained for many patients. By 1 year, only 55% of patients were still in NYHA Class III, while 40% had improved to Class II. Only 4 of 29 patients required up titration to 250 mg twice daily to maintain favorable clinical status. The incidence of hepatotoxicity was 9.7%, and no subject required drug discontinuation.

Two retrospective studies have assessed survival of PAH patients treated with bosentan. Two-year survival in both cohorts was similar (89% and 91%, respectively), and markedly improved compared with a survival rate of 57% predicted by the equation formulated by the National Institutes of Health registry. Despite this encouraging data, the retrospective and uncontrolled nature of these bosentan data limit direct comparison to the earlier, prospective study. Of note, a second agent for PAH was required in only a minority of patients. In McLaughlin’s study 10% of the patients required concurrent epoprostenol therapy, and in Sitbon’s study 13% at 12 months (15% at 24 months) required additional therapy. Factors that predicted a worse outcome included NYHA Class IV and 6-minute walk distance below the median (358 meters) at baseline.

The EARLY trial was a 6-month double blind, randomized, placebo-controlled trial dedicated to PAH patients with mild symptomatic disease (NYHA Class II).
Patients were enrolled if they were either treatment naïve or were on stable doses of sildenafil monotherapy. Two primary endpoints, hemodynamic (mean change in pulmonary vascular resistance) and functional (change in 6-minute walk distance), were assessed. While there was a significant reduction in pulmonary vascular resistance for patients on bosentan (placebo-adjusted, –22.6%, 95% CI –33.5 to –10.0, p < 0.0001) the improvement in 6-minute walk distance was not significant (19.1 meters, 95% CI 3.6 to 41.8, p = 0.07). These data suggest a possible benefit of treating early PAH with bosentan.

Three additional studies evaluated the efficacy of bosentan for patients with pulmonary hypertension associated with other clinical entities and age groups. For 19 pediatric patients with PAH related to congenital heart disease, BREATHE-3 showed improved pulmonary hemodynamics after a 12-week open-label trial of bosentan therapy (dosing was adjusted by weight). Approximately 50% of the patients in BREATHE-3 were on concomitant epoprostenol therapy. Two studies have evaluated the use of bosentan in patients with HIV-related PAH. BREATHE-4 showed improved 6-minute walk distance, functional class, hemodynamics, Doppler echocardiographic indices, and quality of life in a 16-week open label study of bosentan therapy. There was a 9% incidence of hepatotoxicity and there were no adverse interactions related to antiretroviral medications. In a long-term (29 ± 15 months) follow up of patients with HIV-related PAH, Degano et al demonstrated sustained clinical and functional improvements. Of note, 10 of 38 patients undergoing repeat catheterizations had normalization of their pulmonary hemodynamics on bosentan. BREATHE-5 evaluated bosentan therapy in 54 adult patients with PAH due to congenital heart disease and Eisenmenger’s syndrome. All subjects were NYHA Class III, and the study used a randomized double-blinded placebo-controlled approach over 16 weeks. Bosentan therapy improved hemodynamics and exercise capacity in this clinical sub-group as well.

In non-WHO Group 1 pulmonary hypertension, bosentan has also shown to improve functional capacity and symptoms in 3 prospective studies enrolling patients with pulmonary hypertension secondary to inoperable thromboembolic disease. Contrary to its beneficial effects in PAH of WHO Group 1 and thromboembolic disease, bosentan seems to lack efficacy in pulmonary hypertension secondary to left ventricular failure. In a recent double-blind, randomized study evaluating non-invasive (echocardiographic) parameters of hemodynamics in patients with pulmonary hypertension secondary to left ventricular dysfunction, bosentan did not improve any endpoint and was associated with more frequent adverse effects. Similarly, bosentan was not beneficial in patients with severe COPD.

These studies emphasize the importance of establishing the correct diagnosis prior to institution of any therapy for pulmonary arterial hypertension. All patients must have 1) measurement of pulmonary hemodynamics via right heart catheterization, 2) differentiation between WHO Group 1 and non-Group 1 forms of pulmonary hypertension, and 3) correct utilization of pharmacologic therapies, as different treatments need to be applied for different forms of pulmonary hypertension.

**Bosentan in combination therapy for PAH**

PAH patient quality of life and survival remains poor despite the tremendous medical advances with monotherapy. The desire to further improve quantity and quality of life has led to the study of combination therapy. Bosentan has been used in combination with other several classes of PAH therapies, specifically prostacyclin analogues and PDE5 inhibitors.

**Bosentan and prostacyclin analogues**

There have been 5 clinical trials investigating the efficacy and safety of combining bosentan and prostanoids. The first of these was open-label, and examined the addition of bosentan to either inhaled iloprost or oral beraprost (maximum tolerated dose) in 20 PAH patients. The combined therapy was well tolerated and there was significant improvement in the distance walked in 6 minutes, as well as in parameters of exercise testing (maximal oxygen consumption, anaerobic threshold, oxygen pulse, ventilatory efficacy and peak systolic blood pressure during exercise).

The first placebo-control trial of add-on therapy was the 16-week BREATHE-2 study. Thirty-three PAH patients (IPAH or connective tissue disease-related PAH) already receiving intravenous epoprostenol, had either bosentan or placebo added. At 16 weeks there was a trend toward hemodynamic improvement, but no significant change in NYHA Class or exercise capacity. In the bosentan arm of the study, leg edema was more frequent (27% vs 9% with placebo), but otherwise there was no difference in side effect profile. In addition, the three deaths occurred in the combination arm. This study, however, was not powered to detect differences in efficacy, or survival.
The multicenter STEP trial added iloprost or placebo to 67 NYHA Class III or IV PAH patients stably maintained on bosentan. The primary endpoint, postinhalation 6-minute walk distance improved by 26 meters (placebo-adjusted, \( p = 0.051 \)) at week 12. NYHA Class, time to clinical worsening, and post inhalation hemodynamics also improved significantly in patients receiving iloprost. The combination appeared to be safe and well tolerated. A second trial, COMBI, enrolled stable idiopathic PAH patients on bosentan, randomizing them to iloprost or placebo as a second agent. With the assumption that iloprost would improve the 6-minute walk distance (the primary end point) to the magnitude it improved as monotherapy, the study aimed at enrolling 72 patients, but was terminated because at the interim analysis of 40 patients the improvement was not significant enough to continue the trial. Interestingly, as in the STEP trial, the three patients who showed significant deterioration in all objective outcomes were in the combination arm.

Lastly, in an open-label trial, bosentan addition was studied in 16 PAH patients stable on either inhaled or intravenous iloprost, or oral beraprost. The combination improved the average 6-minute walk distance significantly, as well as echocardiographic indices of right ventricular function. Nine patients had an improvement in NYHA Class and effects were sustained at 6 months and longer.

**Bosentan and PDE5 inhibitors**

The combination of bosentan and PDE5 inhibitors is theoretically appealing due to their ease of administration (oral) and favorable side effect profiles when used individually. Unfortunately, due to pharmacodynamic interactions (see Drug interactions), study of this has been largely avoided. The EARLY trial included 29 patients in the bosentan arm who were taking sildenafil. In post hoc analysis, the addition of bosentan was accompanied by a 20% improvement in pulmonary vascular resistance and delayed time to clinical worsening. No significant improvement in 6-minute walk distance was found. Thus, despite the potential for altered drug levels, this preliminary evidence suggests that further study of bosentan-sildenafil combination therapy may be indicated.

**Transitioning from other PAH therapies to bosentan**

Transitioning patients onto oral therapy from parental forms of therapy is an attractive goal for our patients with PAH. The first study to evaluate this took 4 patients with normal hemodynamics on epoprostenol and transitioned them successfully to oral bosentan and they remained stable. A subsequent study evaluated 3 children who had normal hemodynamics on epoprostenol and showed that these children after having been switched to bosentan remained stable for a full 1-year study period. However, subsequent studies that evaluated patients on parental prostanoids that did not normalize their pulmonary hemodynamics, only three-quarters transitioned successfully to bosentan and of those that transitioned more than 60% on bosentan therapy alone deteriorated within 3 to 16 months after the prostanoids were stopped. Therefore the current recommendation is that transitioning from prostaglandins to bosentan only be considered in patients who have normalized their pulmonary hemodynamics and who are under close observation.

**At the bedside: clinical application in practice**

There is arduous debate among PAH specialists regarding which therapy is most appropriate for which PAH patient. Preliminary results from the REVEAL registry, presented at the American College of Chest Physicians meeting in October 2007, give us a glimpse of current clinical practice. Among the first 1226 PAH patients enrolled, only 47% were being treated with monotherapy (bosentan 13%; sildenafil 13%; epoprostenol iv 8%; sitaxsentan 2%, and calcium channel blockers 4%). 36% received 2-drug combination therapy (epoprostenol iv + sildenafil 8%; bosentan + sildenafil 8%; bosentan + epoprostenol 3%; bosentan + inhaled iloprost 3%; and sildenafil + inhaled iloprost 2%), and 9% received 3 or more PAH-specific medications. Therefore, in the absence of rigorous evidence supporting multi-drug therapy, a diverse array of combination strategies has emerged into clinical practice.

In our experience, the selection of therapy must take into consideration an individual’s disease severity, rapidity of progression and signs of poor prognosis. For patients in NYHA Classes II and III, monotherapy with bosentan is often an appropriate first step, assuming that the patient is not at increased risk for adverse effects (see Safety and tolerability). We agree that, despite its approval status for NYHA Class III and IV patients, the use of bosentan monotherapy for NYHA Class IV patients is not advisable, because the onset of improvement may take up to 6 weeks (in the first 4 weeks patients will be on the low dose of 62.5 mg twice a day). Once patients are on oral therapy, frequent (every 1 to 3 months) monitoring of symptoms and documentation of NYHA classification is indicated. Demonstration of
clinical worsening or adverse effects obviously necessitates immediate re-evaluation of therapeutic approach.

**Conclusions, optimizing selection and use in therapy**

The interaction between ET-1 and its receptors play a central role in the maintenance of pulmonary vascular homeostasis. Dysregulated endothelin biology is characteristic of the remodeled pulmonary arterioles that underlie PAH. Since their original description in the 1990s, ERAs such as bosentan, and more recently sitaxsentan and ambrisentan, have contributed to improved function and quality of life for patients with PAH.

Bosentan is approved for use as initial therapy for patients with NYHA Class II–IV PAH, although current expert opinion does not recommend its use as monotherapy for NYHA Class IV patients. The recommended dose for bosentan in adults is 62.5 mg twice daily for 4 weeks and then increased to 125 mg twice daily with long-term monthly monitoring of liver function tests. In PAH patients taking additional therapies with potential drug-drug interactions, especially warfarin, PDE5 inhibitors and oral contraceptives, consideration of dose modifications (or avoidance of interacting medications) must be made.

Many questions about ERA therapy remain unanswered and deserve further study; these include exploration of the pharmacogenomics of these medications, determination of long-term response to therapy, improved insight into the importance of receptor selectivity, and experience with effective combination therapy. Despite the ongoing unanswered questions, the rapid translation of basic science into applicable and efficacious therapies – as demonstrated with bosentan – for patients with PAH has had a tremendous impact for caring for these patients.

**Disclosures**

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**References**


