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SUMMARY OF KEY ARTICLES

Clinical Perspectives in Pulmonary Arterial Hypertension

INTRODUCTIONS BY
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INTRODUCTION

Clinical Perspectives in Pulmonary Arterial Hypertension

Pulmonary hypertension comprises a large and diverse group of disorders whose recognition has grown substantially over the past 25 to 30 years.

Increased understanding of the disease and its potential causes has given rise to a classification system that has evolved in step with the knowledge base about pulmonary hypertension. The first classification system consisted of two categories: primary pulmonary hypertension and secondary pulmonary hypertension.[1] At the 4th World Symposium on Pulmonary Hypertension in 2008, international authorities in the field approved the latest iteration of the classification system, which now encompasses five categories and more than two dozen subgroups.[2]

Pulmonary arterial hypertension (PAH) can be difficult to diagnose. A condition that overlaps the medical specialties of cardiology and pulmonology, diagnosis and evaluation of PAH require an understanding of lung function, pulmonary vascular function, and cardiac function. Collaboration between the specialties is essential to provide the best care possible for patients with PAH, functional class II, III, IV.

Recently published clinical guidelines for management of PAH emphasize the importance of an evidence-based treatment algorithm.[3] The guidelines cite several therapies that can contribute to an evidence-based treatment algorithm, including background therapies, intravenous and subcutaneous prostanoids, and oral agents including phosphodiesterase inhibitors and endothelin-receptor antagonists.

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Managing PAH

A Cardiologist's Perspective

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Pulmonary arterial hypertension (PAH) is a rare disorder, but perhaps not as rare as once believed. Historically, PAH epidemiology has often been characterized as 1 or 2 per million. However, evidence from a French registry suggests the prevalence of about 15 per million.[1]

The more contemporary data on PAH epidemiology makes two key points:

- Far more people are affected by the condition than previously recognized.
- Clinicians should remain vigilant for the possibility of PAH when evaluating patients for dyspnea.

Even with the increased prevalence, PAH does not have a mandate for routine screening in clinical practice. Screening might be appropriate for specific subgroups of patients who have an increased risk of PAH, such as patients with scleroderma.

RECOGNITION

Diagnosis, evaluation, and treatment of PAH overlap the medical specialties of cardiology and pulmonology.[2] Physicians in both specialties have a role in the care of patients with PAH, and patients benefit from a collaborative approach to clinical management. The other categories included in the classification system have features that require more or less involvement of one specialty.

Cardiologists are among the first physicians who see patients with PAH during the initial evaluation. In that respect, cardiologists have a unique opportunity to identify the patients earlier, after excluding more common potential causes of symptoms.

Regardless of when cardiologists have their first patient contact, they have a prominent role in the workup for PAH. Echocardiography is a principal screening tool for the condition. It is often the initial study that leads to the consideration of this diagnosis. In addition to the anatomic and symptomatic information, pulmonary pressure values provide important clues to PAH. More often than not, a cardiologist will perform right heart catheterization, which is the definitive evaluation for diagnosis of PAH.

THERAPY

A key consideration in constructing a clinical algorithm for PAH is the severity of the condition. Newly diagnosed patients with right heart failure, dyspnea at rest, and poor hemodynamics often

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A Pulmonologist's Perspective

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The largest category of pulmonary hypertension is pulmonary arterial hypertension (PAH), which has been the focus classification since the first system was approved in 1973.[1] This category, often called group 1, includes idiopathic PAH, heritable PAH, and multiple conditions and risk factors associated with PAH. One of the fastest growing subgroups within group 1 is PAH associated with drugs and toxins. In particular, use of methamphetamines has increased in prominence as a risk factor for PAH.

RECOGNITION AND AWARENESS

Pulmonologists often are the first point of contact for patients with PAH. Patients seek out pulmonary specialists because the principal symptom of PAH is dyspnea. The key to diagnosis is clinical suspicion. Although dyspnea has many potential causes, including more common diseases such as asthma or chronic obstructive pulmonary disease (COPD), clinicians should remain aware of the possibility that PAH is the underlying problem, particularly as other potential causes are excluded.

Misdiagnosis poses a major challenge to effective clinical management of PAH. Failure to diagnose PAH promptly has significant implications for a condition that already has a poor prognosis and high mortality. Emerging data have suggested substantial delays between onset of symptoms and diagnosis of PAH, causing patients to endure unnecessary morbidity and perhaps giving the disease a window of opportunity for progression.

EVIDENCE-BASED TREATMENT

More than a half-dozen therapies have approval for treatment of PAH. Current clinical guidelines for management of the condition emphasize the importance of an evidence-based treatment algorithm.

Strength of clinical data should always have a key influence on therapeutic decision-making related to PAH. Among currently available therapies, the endothelin receptor antagonist bosentan offers an example of an agent that has accumulated considerable data in clinical research and in clinical practice. Clinical studies of bosentan have yielded short-term data (12-15 weeks), 6-month data, and now long-term evidence of the drug's safety and efficacy in patients with PAH functional class II, III, IV.[2]

The evidence base for a therapy should not begin and end with data from pivotal clinical trials. Experience gained from

Continued on page 4

Managing PAH: A Cardiologist's Perspective (continued)

begin treatment with parenteral prostanoids. However, patients with such advanced disease at diagnosis constitute a small portion of the PAH patient population.

More commonly, newly diagnosed patients with PAH have less severe symptoms. For those patients, oral therapy and close follow-up represent an appropriate approach to treatment. Several US Food and Drug Administration-approved medications are available for initiating therapy in newly diagnosed patients. Based on the EARLY trial, for patients with functional class II PAH, bosentan offers a good option for first-line oral therapy. The agent has a substantial clinical experience to support its safety and efficacy in patients with PAH, functional class II, III, IV.

FOLLOW-UP

Because PAH is fairly uncommon, physicians in the community may often have limited experience in diagnosing and treating the condition. Referral to a specialized center for pulmonary hypertension should be considered. A collaborative approach involving a referring physician and specialists in PAH serves the patient well and helps ensure the close follow-up required for a complex and difficult-to-manage condition. ■

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Managing PAH: A Pulmonologist's Perspective (continued)

treatment of thousands of patients in clinical practice should be weighed alongside results of clinical trials, which may only include a few hundred patients. Since its approval for PAH in 2001, bosentan has accumulated clinical experience that encompasses tens of thousands of patients.

Recently approved clinical guidelines for management of PAH cite several therapies that could contribute to an evidence-based treatment algorithm.[3]

CANDIDATES FOR THERAPY

Many patients in group 1 (functional class II, III, IV) of the pulmonary hypertension classification system may benefit from treatment with bosentan. Disorders included in group 1 share pathogenetic and histopathologic features. Intuitively, the patients stand to benefit from a therapy that targets a specific pathway.

Multiple subgroups of patients with PAH have been evaluated to determine whether endothelin inhibition offers more or less benefit to certain patients. The evidence accumulated to date suggests that patients in many subcategories of group 1 (functional class II, III, IV) may benefit from treatment with bosentan. ■

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Clinical Classification of Pulmonary Arterial Hypertension

Key Point: Group 1 in the updated (2008 Dana Point) clinical classification of pulmonary hypertension focuses on pulmonary arterial hypertension. Pivotal trials for PAH therapies have focused on patients in group 1 of this updated classification.

Based on Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol*. 2009;54(suppl 1):S43-S54.

Since first introduced in 1973, classification of pulmonary hypertension has undergone several revisions. The initial classification schema comprised of only two categories: primary pulmonary hypertension (PPH) and secondary pulmonary hypertension. Categorization depended on the presence or absence of identifiable causes or risk factors.[1,2]

The original classification remained unchanged for 25 years. In 1998, participants at the 2nd World Symposium on Pulmonary Arterial Hypertension adopted the so-called "Evian classification," so named because of the meeting venue in Evian, France. The 1998 criteria established categories of pulmonary hypertension based on shared pathologic and clinical features, as well as similar therapeutic options.[3]

The Evian classification expanded the classification to five major groups, which allowed clinical investigators to study well-defined patient populations with a shared pathogenesis. The classification played a major role in clinical trials that led to the approval of eight different medications for pulmonary hypertension.[4]

At the 3rd World Symposium on Pulmonary Arterial Hypertension held in Venice, Italy, in 2003, the Evian classification system underwent modest revisions, the most notable being the abandonment of PPH in favor of five categories: idiopathic pulmonary arterial hypertension (PAH); familial PAH; associated PAH, the designation for PAH that occurs in association with other conditions, such as connective tissue disease or human immunodeficiency virus (HIV) infection; and miscellaneous categories of PAH.[5]

Five years passed before another revision was made in the classification system, which occurred in 2008 at the 4th World Symposium on Pulmonary Arterial Hypertension held in Dana Point, California.[4] Participants at the symposium maintained five major groupings, but several groups underwent substantive revisions (**Table 1**).

The 2008 classification system was published earlier this year in a supplement to the *Journal of the American College of Cardiology*.[4] The discussion that follows highlights some of the key points of Group 1 PAH.

World Health Organization (WHO) Group 1: PAH

Since 1973, the classification has focused on PAH, and the 2008 version maintains that focus. The group now comprises 15 subgroups (not including 1').

TABLE 1. Updated Clinical Classification of Pulmonary Arterial Hypertension (WHO Group 1) (Dana Point, 2008) Main modifications to the previous Venice classification are in bold.

1.	Pulmonary arterial hypertension (PAH)
1.1.	Idiopathic PAH
1.2.	**Heritable**
1.2.1.	**BMPR2**
1.2.2.	**ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)**
1.2.3.	**Unknown**
1.3.	Drug- and toxin-induced
1.4.	Associated with
1.4.1.	Connective tissue diseases
1.4.2.	HIV infection
1.4.3.	Portal hypertension
1.4.4.	Congenital heart diseases
1.4.5.	**Schistosomiasis**
1.4.6.	**Chronic hemolytic anemia**
1.5.	Persistent pulmonary hypertension of the newborn

ALK1=activin receptor-like kinase type 1; BMPR2=bone morphogenetic protein receptor type 2; HIV=human immunodeficiency virus.
Adapted from: Simonneau et al.[4] Used with permission.

Group 1 includes both idiopathic and heritable PAH (subcategories 1.1 and 1.2) and accounts for the largest segment of the patient population with pulmonary hypertension. Idiopathic PAH refers to sporadic disease with no family history or identified risk factors. Approximately 70% of patients in subcategory 1.2 have germ-line mutations in the bone morphogenetic protein receptor type 2 (*BMPR2*) gene. However, as many as 40% of patients with apparently idiopathic PAH also have *BMPR2* mutations. Moreover, as many as 30% of families with PAH have no identified *BMPR2* mutations. Consequently, the distinction between idiopathic and familial PAH was artificial, a factor that led directly to the decision to replace the term "familial" with "heritable" in the 2008 revision.

Clinical Classification of Pulmonary Arterial Hypertension (continued)

Table 2. Updated Risk Factors for and Associated Conditions of PAH

Definite	Possible
Aminorex	Cocaine
Fenfluramine	Phenylpropanolamine
Dexfenfluramine	St. John's Wort
Toxic Grapeseed oil	Chemotherapeutic agents
	SSRI
Likely	**Unlikely**
Amphetamines	Oral contraceptives
L-tryptophan	Estrogen
Methamphetamines	Cigarette smoking

PAH=pulmonary arterial hypertension; SSRI=selective serotonin reuptake inhibitor.
Source: Simonneau et al.[4] Used with permission.

Subcategory 1.3 includes drug- and toxin-induced PAH. To help understand the strength of evidence with identified associated factors and their role with the development of pulmonary arterial hypertension, four categories have been identified: definite, likely, possible, and unlikely (**Table 2**). Aminorex, fenfluramine, dexfenfluramine, and toxic rapseed oil comprise the definite category while amphetamines, L-tryptophan, and methamphetamines are included in the likely category.

Subcategory 1.4 comprises PAH associated with other conditions. The subcategory is further divided into six groups representing the most common associated conditions: connective tissue diseases, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis, and chronic hemolytic anemia.

The last PAH-specific subgroup is 1.5, persistent pulmonary hypertension of the newborn. The subcategory of 1 has no additional subgroups.

CONCLUSION

Participants in the 2008 classification of PAH sought to incorporate the most recent evidence and to clarify ambiguities in previous iterations. At the same time, the classification is the most comprehensive to date, which should prove useful in clinical practice. ■

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Targeting Endothelin-1 in PAH With Bosentan

Key Point: This pivotal trial with bosentan was the first double-blind placebo controlled study to investigate the role of blocking endothelin in pulmonary arterial hypertension (PAH). The positive impact on exercise capacity, hemodynamics, and functional class built the foundation for further study with an oral endothelin receptor antagonist medication for the treatment of PAH.

Based on Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. *Lancet*. 2001;358:1119-1123.

Evidence that endothelin plays a key role in the development and progression of pulmonary arterial hypertension (PAH) provided a rationale for evaluating endothelin inhibition as a therapeutic strategy for patients with this disease. In an early test of the endothelin hypothesis, the dual endothelin-receptor antagonist bosentan was evaluated in a randomized, placebo-controlled clinical trial.[1]

METHODS

The study included 32 patients with PAH or PAH associated with scleroderma. They were randomly assigned 1:2 to placebo or to bosentan at a dose of 62.5 mg BID for 4 weeks and then 125 mg BID for a total of at least 12 weeks of therapy. The primary endpoint was change in exercise capacity from baseline to the end of treatment. Secondary endpoints included changes in cardiopulmonary hemodynamics, Borg dyspnea index, WHO functional class, and withdrawal because of clinical worsening.

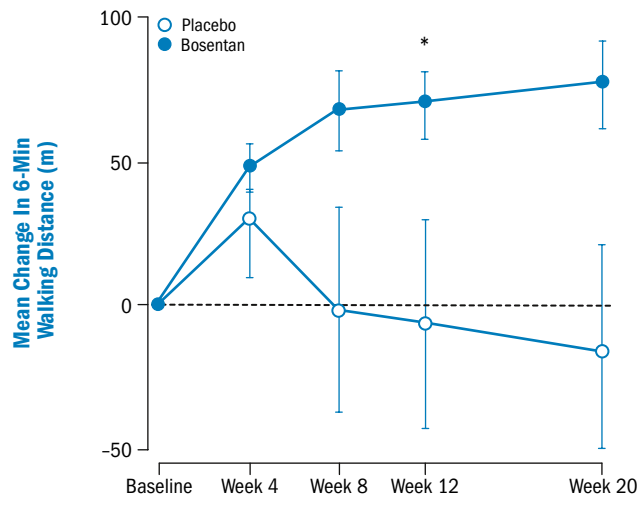
RESULTS

At baseline the 6-minute walk distance averaged 360 meters in the bosentan group and 355 meters in the placebo group.

After 12 weeks of treatment, bosentan-treated patients had a 70-meter improvement in 6-minute walk distance compared with no change in the placebo group ($P=0.021$) (**Figure 1**). All patients were in functional class III at baseline. In the bosentan group, nine of 21 patients improved to class II and the other 12 remained stable in class III. In contrast, one of 11 patients in the placebo group improved to class II, eight remained in class III, and two deteriorated to class IV ($P=0.019$ versus bosentan).

Treatment with bosentan significantly increased the time to clinical worsening compared with placebo ($P=0.033$). All secondary endpoints favored treatment with bosentan compared with placebo ($P=0.035$ to $P<0.001$).

Figure 1. Change in Six-Minute Walking Distance From Baseline to Week 20



Source: Channick et al. Used with permission.

Table 1. Haemodynamic effects of placebo and bosentan at week 12

	Change from baseline		Difference between treatments	
	Placebo (n=10)	Bosentan (n=20)	Difference (95% CI)	p
Variable				
Cardiac index (mean [SE], L min–1m–2)	0·5 (0·1)	0·5 (0·1)	1·0 (0·6 to 1·4)	<0·001
Pulmonary vascular resistance (mean [SE], dyn s cm-5)	191 (74)	223 (56)*	415 (608 to -221)	0·001
Pulmonary artery pressure (mean [SE], mm Hg)	5·1 (2·8)	1·6 (1·2)	6·7 (11·9 to -1.5)	0·013
Pulmonary capillary wedge pressure (mean [SE], mm Hg)	3·9 (1·8)	0·1 (0·8)*	3·8 (7·3 to -0·3)	0·035
Mean right atrial pressure (mean [SE], mm Hg)	4·9 (1·5)	1·3 (0·9)*	6.2 (-9·6 to -2·7)	0·001

*Bosentan (n=19).
Source: Channick et al. Used with permission.

Treatment with bosentan significantly improved hemodynamics from baseline to week 12 compared with the placebo group. The bosentan group demonstrated improvements in cardiac index, pulmonary vascular resistance, mean pulmonary arterial pressure, and mean right atrial pressure (**Table 1**).

The number, nature, and severity of adverse events were similar between the bosentan and placebo groups (see full safety profile on pages 15-16).

DISCUSSION

Chronic treatment with the oral dual endothelin-receptor antagonist bosentan significantly improved exercise capacity and cardiopulmonary hemodynamics in patients with PAH. Bosentan treatment consistently improved all clinical endpoints evaluated in the study. Though limited by the small number of patients, the results suggest that endothelin plays an important role in the pathogenesis and evolution of pulmonary hypertension. Use of a dual endothelin-receptor antagonist, such as bosentan, would appear to be a rational approach to the treatment of pulmonary arterial hypertension. ■

Targeting Endothelin-1 in PAH With Bosentan (continued)

Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) in patients with WHO Class II-IV symptoms, to improve exercise ability and decrease the rate of clinical worsening. Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these potential benefits are sufficient to offset the risk of liver injury in WHO Class II patients, which may preclude future use as their disease progresses.

Important safety information
Because of the associated risks, Tracleer may be prescribed only through the Tracleer Access Program.

Potential for serious liver injury (including, after prolonged treatment, rare cases of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring)—Liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter.

High potential for major birth defects—Pregnancy must be excluded and prevented through the use of reliable forms of birth control; monthly pregnancy tests should be obtained.

Contraindicated for use with cyclosporine A and glyburide.

Please see accompanying full prescribing information on back cover and the safety profile information included on pages 15 and 16.

REFERENCE

1. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endotheln-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo-controlled study. *Lancet*. 2001;358:1119-1123.

Bosentan Therapy For Pulmonary Arterial Hypertension

Key Point: This pivotal trial was the second and larger (213 patients), double-blind placebo controlled study with the use of a dual endothelin receptor antagonist, bosentan, for PAH. This was the first study in PAH to assess time to clinical worsening, an important endpoint in PAH clinical trials.

Based on Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:896-903.

An accumulation of evidence has implicated endothelin 1 in the pathogenesis of pulmonary arterial hypertension (PAH). Bosentan, an oral dual endothelin-receptor antagonist, improved exercise capacity and cardiopulmonary hemodynamics in a 12-week clinical trial involving patients with World Health Organization (WHO) functional class III PAH. At a dosage of 125 mg BID, bosentan was well tolerated.[1]

The Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE-1) investigated the effect of bosentan on exercise capacity in a larger number of patients with PAH, including patients with functional class IV PAH.[2] BREATHE-1 also compared the relative efficacy and safety of two dosages of bosentan (125 and 250 mg BID).

METHODS

BREATHE-1 included patients who had class III to IV PAH despite treatment with anticoagulants, vasodilators, diuretics, cardiac glycosides, or supplemental oxygen. All patients had either primary PAH or PAH associated with connective tissue disease. Eligibility criteria for BREATHE-1 included a baseline 6-minute walking distance of 150 to 450 meters, a resting pulmonary artery pressure >25 mm Hg, a pulmonary capillary wedge pressure of <15 mm Hg, and pulmonary vascular resistance >240 dyn/s/cm^{-5}. The protocol excluded patients who had begun or discontinued any therapy for PAH within a month before screening for the trial or who had received or had been scheduled to receive long-term treatment with epoprostenol within 3 months of screening.

Investigators at 27 centers in Europe, North America, Israel, and Australia enrolled 213 patients who were randomized to placebo or to bosentan at a dosage of 62.5 mg BID for 4 weeks, followed by 125 or 250 mg BID for 12 weeks. Patients randomized within the first 2 months of the study participated in a second phase designed to collect an additional 12 weeks of data on safety and efficacy. At the end of the study, all patients were eligible to enter an open-label extension study of bosentan.

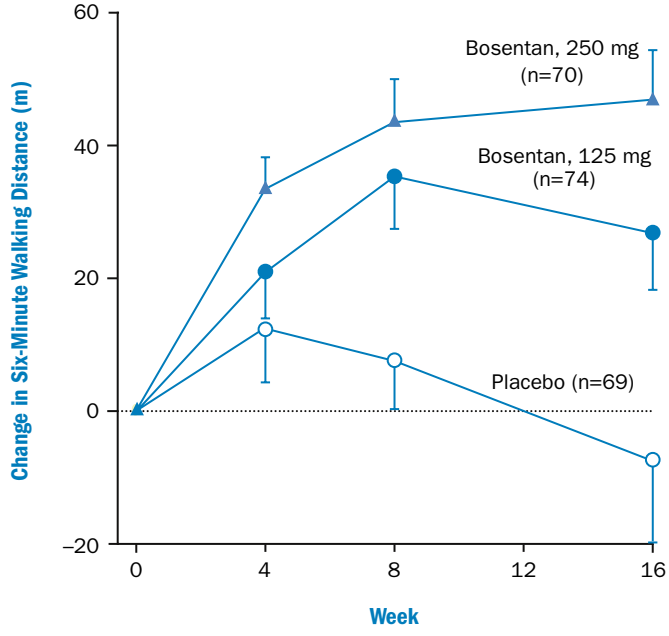
The primary efficacy endpoint was the change from baseline to week 16 in exercise capacity (6-minute walk test). Secondary endpoints included change in Borg dyspnea index, change in WHO functional class, and time to clinical worsening. During the second phase of the study, patients were evaluated after 22 and 28 weeks of therapy.

RESULTS

The study population consisted of 144 patients randomized to bosentan and 69 patients to placebo. After the 4-week bosentan run-in phase, 74 patients in the bosentan group were assigned to the 125 mg BID dosage and 70 to the 250 mg BID dosage. Walking distance was somewhat greater with 250 mg BID, but the potential for increased liver injury causes this dose to not be recommended.

At the end of the first phase of the study, combined results of the bosentan groups showed a mean increase of 36 meters in the walk test compared with an 8-meter reduction in the placebo group. The 44-meter net difference was statistically significant ($P<0.001$) (**Figure 1**).

Figure 1. Mean (±SE) Change in Six-Minute Walking Distance From Base Line to Week 16 in the Placebo and Bosentan Groups



Source: Rubin et al.[2] Used with permission.

Both doses of bosentan significantly improved exercise capacity compared with placebo, but the higher dosage resulted in greater improvement (54 meters vs 35 meters with the lower dose). However, investigators did not observe a dose-response relationship.

Bosentan Therapy For Pulmonary Arterial Hypertension (continued)

Subgroup analyses demonstrated significant improvement in the walk test with bosentan regardless of sex, cause of disease, associated congenital heart defect, time from diagnosis, baseline walk-test performance, and baseline hemodynamics.

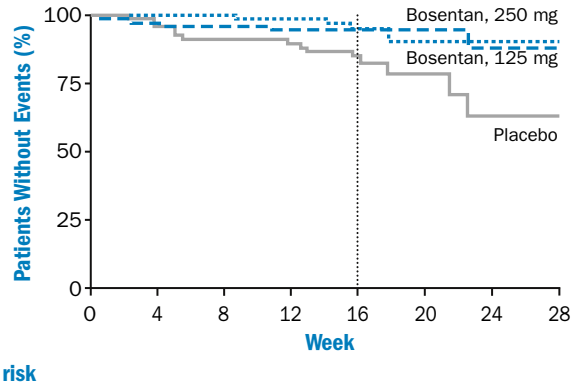
Bosentan had a similar effect in patients with primary PAH and those with PAH associated with connective tissue disease. There were no apparent differences in treatment effects among subgroups, as the study was not designed to detect such differences. However, the dual endothelin-receptor antagonist improved 6-minute walk distance by 46 meters in 102 patients with primary PAH compared with a 5-meter decline among 48 patients with primary PAH in the placebo group. Bosentan therapy improved walk distance by 3 meters among 33 patients with PAH associated with connective tissue disease, whereas 14 similar patients in the placebo group had a 40-meter deterioration in walk distance.

The Borg dyspnea index decreased by an average of 0.1 in patients assigned to the lower dosage of bosentan and by an average of 0.6 in patients assigned to 250 mg BID. The index increased by an average of 0.3 in the placebo group. The placebo-corrected improvement was statistically significant with the higher dosage of bosentan (P=0.012), but not the 125 mg BID dosage (**Figure 2**).

For both doses of bosentan combined, 42% of patients had improvement in WHO functional class compared with 30% of placebo-treated patients. Bosentan significantly increased the time to clinical worsening compared with placebo (P=0.002). The degree of improvement was similar with both dosages of bosentan.

Adverse events were similar and occurred in similar proportions of patients in the bosentan groups and the placebo groups, with the exception of abnormal hepatic function, which was more common in the 250mg group (14%). Abnormal hepatic function was observed in three out of the seventy four patients (4%) in the 125 mg bosentan group (see full safety profile on pages 15-16).

Figure 2. Kaplan–Meier Estimates of the Proportion of Patients With Clinical Worsening



Number at risk								
Placebo	69	68	63	62	48	10	7	3
Bosentan, 125 mg	74	72	71	70	55	18	14	7
Bosentan, 250 mg	70	70	70	68	48	13	11	6

Source: Rubin et al.[2] Used with permission.

DISCUSSION

Both dosages of bosentan proved superior to placebo. However, the increased frequency of abnormal liver function with the higher dosage suggests that 125 mg BID might be the preferred dosage.

Overall, the results confirmed the therapeutic potential of endothelin-receptor blockade for primary PAH. ■

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2. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:896-903.

Treatment of Functional Class II PAH With Bosentan

Key Point: This is the only PAH pivotal clinical trial with an exclusively mildly symptomatic (functional class II) population. The results demonstrate that if left untreated, mildly symptomatic PAH (FC II) can progressively worsen despite the maintenance of exercise capacity.

Based on Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): A double-blind, randomised controlled trial. *Lancet*. 2008;371:2093-2100.

Evaluation of treatments for pulmonary arterial hypertension (PAH) has focused on patients with advanced disease (functional classes III and IV). Observational studies had suggested a potential advantage to treating the disease earlier in the clinical course.[1,2] However, the observations had not been tested in a clinical trial involving less compromised patients.

Endothelin plays a key role in the evolution and progression of PAH, exerting both vasoconstrictor and mitogenic effects via vascular smooth muscle. Bosentan is an orally active inhibitor of the receptor isoforms endothelin A and endothelin B. The drug improved exercise capacity and hemodynamics and slowed PAH progression in two pivotal clinical trials, which predominantly involved patients with functional class III-IV PAH.[3,4]

The EARLY trial,[5] a multicenter international investigation, evaluated the efficacy of bosentan in patients with World Health Organization functional class II PAH.

METHODS

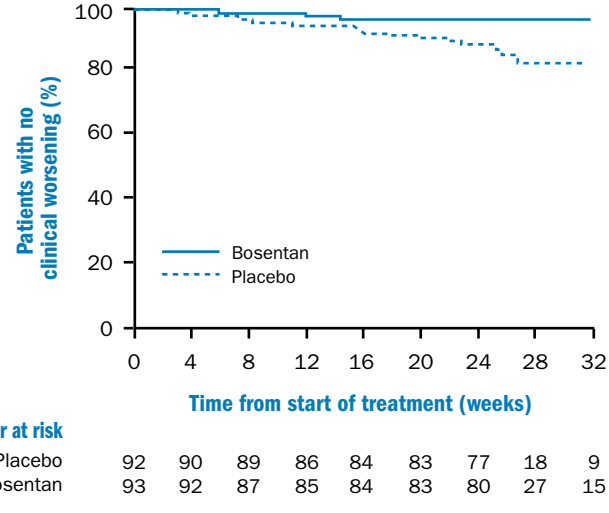
Investigators at 52 sites in 21 countries enrolled 185 patients age 12 years or older, all of whom were mildly symptomatic (functional class II). Eligible patients had a 6-minute walk distance <80% of normal predicted value or <500 meters associated with a Borg dyspnea index ≥2, as well as pulmonary vascular resistance ≥320 dyn/s/cm^5. Entry criteria allowed for patients with idiopathic PAH, familial PAH, or PAH associated with HIV infection, anorexigen use, atrial septal defect <2 cm in diameter, ventricular septal defect <1 cm in diameter, patent ductus arteriosus, or connective-tissue or autoimmune diseases.

The protocol prohibited use of approved treatments for PAH, including prostanoids and other endothelin receptor antagonists. Because sildenafil was approved for treatment of PAH after the trial began, the protocol was amended to permit use of the drug. Concomitant use of anticoagulants was allowed, as was stable-dose calcium channel antagonists initiated at least 1 month before randomization in the EARLY trial.

Patients were randomized to bosentan or placebo for 6 months of double-blind treatment. Treatment with bosentan began at a dose of 62.5 mg BID, titrated after 4 weeks to 125 mg BID, except for patients with body weight <40 kg, who remained on the starting dose.

The trial had two co-primary endpoints: change from baseline to 6 months in pulmonary vascular resistance at rest and in the 6-minute walk test. Secondary endpoints included time to clinical worsening (**Figure 1**), change from baseline to 6 months in WHO functional class, Borg dyspnea index, total pulmonary resistance, mean pulmonary arterial pressure, cardiac index, and mixed venous oxygen saturation; and other exploratory endpoints include QoL and pro-BNP.

Figure 1. Time to Clinical Worsening



Source: Galiè et al.[5] Used with permission.

RESULTS

Analyses of the co-primary endpoints included 168 patients (80 treated with bosentan) for change in pulmonary vascular resistance and 177 patients (86 in the bosentan group) for the 6-minute walk test.

At 6 months, the mean pulmonary vascular resistance in the bosentan group was 83.2% of the baseline value (95% confidence level [CI], 73.8-93.7). In contrast, pulmonary vascular resistance increased to an average of 107.5% of baseline in the placebo group (95% CI, 97.6-118.4). The difference translated into a net treatment effect of -22.6% (95% CI, -33.5 to -10.0, P<0.0001). The treatment effect was similar after stratification of patients by sildenafil use.

At baseline the 6-minute walk distance averaged 435 meters, further distinguishing the trial from earlier studies involving patients with more symptomatic disease and functional limitation. The mean 6-minute walk distance increased

Treatment of Functional Class II PAH With Bosentan (continued)

by 11.2 meters in the bosentan group (95% CI, -4.6 to 27.0) and decreased by 7.9 meters in the placebo group (95% CI, -24.3 to 8.5). The net treatment effect of 19.1 meters did not achieve clinical significance (95% CI, -3.6 to 41.8, p=0.0758). Stratification by concomitant sildenafil use did not significantly alter the results. A separate analysis by median treatment effect also did not yield statistically significant differences between treatment groups.

The treatment effect on pulmonary vascular resistance was similar in patients with idiopathic PAH and those with other categories of PAH, although the trial was not statistically powered for subgroup analysis.

Treatment with bosentan significantly increased the time to clinical worsening by almost 80%, as reflected in a hazard ratio of 0.227 (95% CI, 0.065-0.798, *P*=0.0114). Patients in the bosentan group also were significantly less likely to have worsening of WHO functional class (*P*=0.0285). The change in Borg index did not differ significantly at 6 months.

The incidence of adverse events was 70% in the bosentan group and 65% in the placebo group. Serious adverse events, including those deemed unrelated to treatment, occurred in 13% of bosentan patients and 9% of placebo-treated patients (see full safety profile on pages 15-16).

DISCUSSION

Results of the EARLY trial demonstrated improvement in pulmonary vascular resistance in patients with mildly symptomatic PAH treated with bosentan. Fewer bosentan-treated patients worsened clinically. Though the trial population comprised less compromised patients with PAH, deterioration still occurred in the placebo group, showing that PAH progresses rapidly, even in less advanced stages.

The treatment effect observed with bosentan has clinical relevance because of previous observations that reduced pulmonary vascular resistance after PAH therapy predicts survival.

The principal limitation of the trial was its length, which might have been insufficient to detect differences in some endpoints. Additionally, the study lacked the statistical power for subgroup analyses.

Collectively, the findings of the EARLY trial suggest that treatment with bosentan might benefit patients with WHO functional class II PAH. ■

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4. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med*. 2002;346:896-903.
5. Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): A double-blind, randomized controlled trial. *Lancet*. 2008;371:2093-2100.

Treatment of Eisenmenger Syndrome with Bosentan

Key Point: Bosentan is the first and only PAH therapy to be studied in a clinical trial with an exclusively dedicated population of PAH associated with congenital heart disease (Eisenmenger Syndrome).

Based on Galiè N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger Syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation*. 2006;114:48-54.

Until recently, no evidence-based approach to treatment existed for advanced pulmonary arterial hypertension (PAH) associated with congenital heart disease, or Eisenmenger Syndrome. The syndrome manifests as a multisystem disorder associated with a variety of life-threatening complications, including hemoptysis, cerebrovascular accidents, brain abscess, cardiac arrhythmias, and syncope.

Eisenmenger Syndrome evolves as the congenital heart defect causes a major left to right shunt, induces severe pulmonary vascular disease and PAH, and finally results in reversal of the direction of shunting and development of cyanosis. The structural abnormalities in lung circulation associated with Eisenmenger Syndrome are histologically similar to those caused by other forms of PAH.

Endothelin 1 appears to have a key role in the pathogenesis of PAH, and elevated concentrations of endothelin 1 have been observed in patients with Eisenmenger Syndrome. Intuitively, inhibition of endothelin 1 would appear to offer a potentially effective therapeutic approach.

Bosentan is an oral dual endothelin-1 receptor antagonist that has demonstrated efficacy in idiopathic PAH and PAH related to connective tissue disease.[1,2] Small, uncontrolled studies have suggested that bosentan may improve exercise capacity and hemodynamics in patients with Eisenmenger Syndrome.[3-6]

The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was the first controlled study of bosentan in patients with Eisenmenger Syndrome.[7]

METHODS

BREATHE-5 included patients older than 12 years with Eisenmenger Syndrome and associated World Health Organization (WHO) functional class III PAH. Presence of the syndrome was established by echocardiography and cardiac catheterization.

Eligibility criteria included systemic pulse oximetry (SpO2) of 70% to 90% at rest with room air and a 6-minute walk distance of 150 to 450 meters. Exclusion criteria included patent ductus arteriosus, complex congenital heart defect, left ventricular dysfunction, restrictive lung disease, obstructive lung disease, and coronary artery disease.

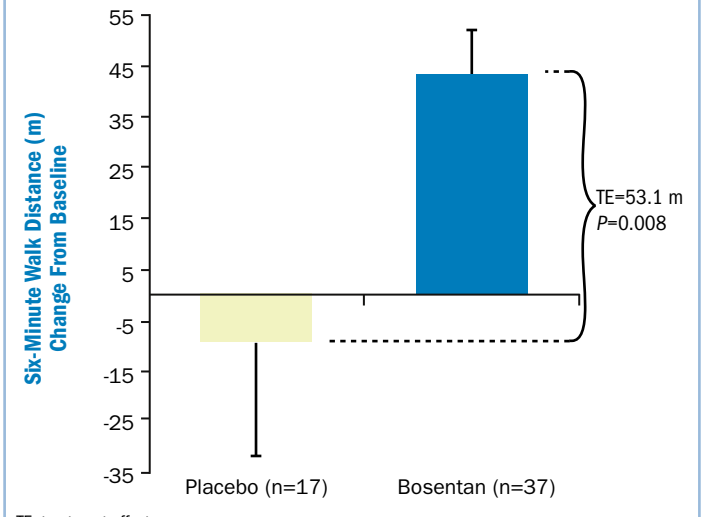
Investigators at 15 centers in Europe, North America, and Australia randomized patients 2:1 to bosentan or placebo. Bosentan therapy began at a dosage of 62.5 mg BID for 4 weeks, followed by 125 mg BID for an additional 12 weeks. Patients who could not tolerate the 125 mg BID dosage could be downtitrated to the starting dosage.

The trial had both a first and a second primary endpoint. The first was a safety endpoint in the form of change in SpO2 from baseline to week 16. The second primary endpoint was the change in pulmonary vascular resistance index (PVRi) from baseline to week 16. Investigators conducted a noninferiority test to compare bosentan and placebo. If the null hypothesis related to SpO2 was rejected, a second test was performed to compare bosentan and placebo with respect to effect on PVRi, defined as (mean pulmonary arterial pressure minus left atrial pressure)/systemic blood flow index X 80.

RESULTS

The trial included 54 patients, 37 randomized to bosentan and 17 to placebo. The patient groups were well matched with respect to baseline characteristics (**Figure 1**).

Figure 1. Change From Baseline of 6-Minute Walk Distance in Placebo and Bosentan Groups



TE=treatment effect.
Source: Galiè et al.[7] Used with permission.

The baseline SpO2 averaged 83.6% in the placebo group and 83.7% in the bosentan group. Direct measurement of SpO2 by left-heart catheterization yielded baseline averages of 82.4% in the placebo group and 80.2% in the bosentan group. The placebo-corrected effect was 1.0 (95% confidence interval [CI],

Treatment of Eisenmenger Syndrome with Bosentan (continued)

-0.7–2.8) >-5, which met the criteria for noninferiority and confirmed that bosentan does not reduce systemic arterial blood oxygen saturation. No patient in either group had as much as a 10% decrease in SpO2 from baseline.

The PVRi increased by 5.4% in the placebo group, but decreased by 9.3% in bosentan-treated patients, resulting in a statistically significant treatment effect (P=0.0383). The systemic vascular resistance index increased by 10.4% in the placebo group and declined by 11.5% in the bosentan group, but the difference did not achieve statistical significance.

The 6-minute walk distance decreased by 9.7 meters in the placebo group and increased by 43.4 meters in the bosentan group. The net treatment effect of 53.1 meters was statistically significant (P=0.008). The treatment effect remained significant in a robustness analysis (P=0.0176).

Two placebo-treated patients improved to functional class II compared with 13 patients in the bosentan group. One patient in each group had deterioration to WHO class IV.

Several adverse events occurred more often with bosentan than with placebo: peripheral edema (19% vs 6%), headache (14% vs 12%), palpitations (11% vs 0%), dizziness (8% vs 6%), and chest pain (8% vs 0%). Severe adverse events were infrequent (8% with bosentan and 18% with placebo). Two patients in each group discontinued because of adverse events (see full safety profile on pages 15-16).

A total of 37 patients (11 placebo, 26 bosentan) who completed randomized therapy entered a 24-week open-label extension study. At the end of the extension phase, placebo-treated patients switched to bosentan had a 33.2-meter improvement in the 6-minute walk distance, and patients originally treated with bosentan maintained the initial effect, increasing the mean difference by 6.7 meters.

DISCUSSION

In this first-ever randomized, placebo-controlled trial for adults with Eisenmenger Syndrome, bosentan significantly improved hemodynamics and exercise capacity without adversely affecting systemic arterial oxygen saturation. The results indicate that bosentan may represent a treatment option for patients with the syndrome. ■

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SAFETY PROFILE

Liver and pregnancy warnings

Because of the risks associated with treatment, the use of Tracleer requires participation in the Tracleer Access Program (T.A.P.®), a restricted distribution program. In order to receive Tracleer, prescribers and patients must enroll in T.A.P. and agree to comply with the requirements of this program.

Tracleer may cause liver damage

- In the Tracleer pivotal clinical trials, Tracleer caused at least 3-fold (upper limit of normal; ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases.
- Because these changes are a marker for potential serious liver injury, liver monitoring of all patients is essential prior to initiation of treatment and monthly thereafter.
- Elevations in aminotransferases require close attention.
- Discontinue Tracleer if aminotransferase elevations are accompanied by signs or symptoms of liver dysfunction or injury or increases in bilirubin ≥2 × ULN.

Liver enzyme elevations: experience and management

- Use of Tracleer should generally be avoided in patients with elevated aminotransferases (>3 × ULN) **at baseline** because monitoring liver injury may be more difficult.
- It is important to adhere strictly to the monthly monitoring schedule for the duration of treatment.
  - —Changes in aminotransferases may occur early or late in treatment.
  - —There have been rare postmarketing reports of liver failure and unexplained hepatic cirrhosis in a setting of close monitoring; the contribution of Tracleer could not be excluded.

Pregnancy must be excluded and prevented

- Tracleer is very likely to produce major birth defects if used by pregnant females, based on animal data.
- To prevent pregnancy, females of childbearing potential must use 2 reliable methods of contraception during treatment and for 1 month after stopping Tracleer.
  - —No other contraception is needed for patients who have a tubal sterilization or Copper T 380A IUD or LNg-20 IUS inserted.
- Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives, should not be used as the sole means of contraception because they may not be effective in patients receiving Tracleer.
- Monthly pregnancy tests should be obtained.

Please see accompanying full prescribing information on back cover

Tracleer aminotransferase (ALT/AST) management[1]

ALT/AST level	Treatment and monitoring recommendations
1 to 3 × ULN	**Continue** to monitor; no change in monitoring schedule or dosage
>3 to ≤5 × ULN	**Confirm** by another test; **if confirmed, reduce the dose or interrupt** treatment and monitor LFT levels every 2 weeks **Continue or reintroduce Tracleer** if levels return to pretreatment levels
>5 to ≤8 × ULN	**Confirm** by another test; if confirmed, stop therapy; monitor LFTs at least every 2 weeks **Consider** reintroduction of therapy if LFTs return to pretreatment levels
>8 × ULN	**Stop** therapy; do not reintroduce

If Tracleer is reintroduced, it should be at the starting dose; aminotransferase levels should be checked within 3 days and thereafter according to the recommendations above.

If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥2 × ULN, treatment should be stopped. There is no experience with the reintroduction of Tracleer in these circumstances.

Safety profile: warnings, precautions, adverse events, and drug interactions

Adverse events occurring in ≥3% of patients treated with Tracleer and morefrequently than the placebo group[1]

Adverse event	Tracleer (n=258)	Placebo (n=172)	Adverse event	Tracleer (n=258)	Placebo (n=172)
Respiratory tract infection	56 (22%)	30 (17%)	Hypotension	10 (4%)	3 (2%)
Headache	39 (15%)	25 (14%)	Sinusitis	9 (4%)	4 (2%)
Edema	28 (11%)	16 (9%)	Arthralgia	9 (4%)	3 (2%)
Chest pain	13 (5%)	8 (5%)	Liver function test abnormal	9 (4%)	3 (2%)
Syncope	12 (5%)	7 (4%)	Palpitations	9 (4%)	3 (2%)
Flushing	10 (4%)	5 (3%)	Anemia	8 (3%)	–

Tracleer: Indicated for PAH WHO functional class II, III, IV

Safety profile when administered with other standard PAH medications in pivotal trials[1]

- Patients receiving Tracleer continued other medications, including anticoagulants, digoxin, diuretics, and vasodilators such as calcium channel blockers and ACE inhibitors.[2,3]
- Patients receiving epoprostenol within 3 months of study screening were ineligible for participation.[2,3]
- In the EARLY trial, both the Tracleer group and the placebo group included some patients on sildenafil at baseline (Tracleer, n=14; placebo, n=15).[4]

Fluid retention[1]

- Peripheral edema is a known clinical consequence of PAH and worsening PAH, and is also a known effect of other endothelin receptor antagonists.
- In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7% (placebo-corrected) of patients.
- There have been postmarketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer.
- If clinically significant fluid retention develops, further evaluation should be undertaken to determine the cause, and the possible need for treatment or discontinuation of Tracleer therapy.

Decreased sperm counts[1]

- In an open-label study (N=25), a decline in sperm count of at least 50% in 25% of Tracleer-treated patients was observed after 3 or 6 months. Sperm count remained in normal range after 6 months, with no changes in sperm morphology, sperm motility, or hormone levels.
- It cannot be excluded that endothelin receptor antagonists such as Tracleer have an adverse effect on spermatogenesis.

Associated with dose-related decreases in hemoglobin[1]

- Decreases in hemoglobin concentration:
  - —Measured 0.9 g/dL (overall mean decrease) for Tracleer-treated patients
  - —Were detected during the first few weeks of treatment
  - —Stabilized by 4 to 12 weeks of treatment
- Monitoring of hemoglobin concentrations recommended after 1 and 3 months, and quarterly thereafter

Pulmonary veno-occlusive disease (PVOD)[1]

- If signs of pulmonary edema occur when Tracleer is administered, the possibility of associated PVOD should be considered and Tracleer should be discontinued.

Tracleer has NO dosing adjustments or clinically relevant interactions with:

Sildenafil[1,4] **Warfarin**[1,4] **Iloprost**[1]

Drug-drug interactions[1]

Tracleer is contraindicated for use with cyclosporine A and glyburide. Tracleer is metabolized by CYP2C9 and CYP3A. Co-administration with agents that are metabolized by these pathways may affect plasma concentrations of one or both agents. When initiating lopinavir/ritonavir and other ritonavir-containing HIV regimens, dosage adjustment of Tracleer is necessary. When co-administered with simvastatin, or other statins that are CYP3A substrates, dosage adjustment of such statins may need to be considered. When co-administered with rifampicin, a CYP3A inducer, liver function should be monitored weekly for the first 4 weeks before reverting to normal (monthly) monitoring. Co-administration of tacrolimus and bosentan resulted in markedly increased plasma concentrations of bosentan in animals; caution should be exercised if they are used together. When co-administered with ketoconazole, a potent CYP3A inhibitor, dosage adjustment of Tracleer may need to be considered. There are no clinically relevant interactions between Tracleer and digoxin, nimodipine, or losartan.

References: 1. Tracleer (bosentan) full prescribing information. Actelion Pharmaceuticals US, Inc. August 2009. **2.** Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet.* 2001;358:1119-1123. **3.** Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med.* 2002;346:896-903. **4.** Galiè N, Rubin LJ, Hoeper MM, et al. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double blind, randomised controlled trial. *Lancet.* 2008;371:2093-2100.

Tracleer® BOSENTAN TABLETS

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