

Pulmonary Arterial Hypertension (PAH) Agents, Oral Review

10/02/2008

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Pulmonary Arterial Hypertension (PAH) Agents, Oral Review

FDA-Approved Indications

Drug	Manufacturer	Indication(s)
ambrisentan (Letairis™) ¹	Gilead Sciences	<ul style="list-style-type: none">Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II or III symptoms, to improve exercise capacity and delay clinical worsening.
bosentan (Tracleer®) ²	Actelion	<ul style="list-style-type: none">Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class III or IV symptoms, to improve exercise ability and decrease the rate of clinical worsening.
sildenafil (Revatio™) ³	Pfizer	<ul style="list-style-type: none">Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability

Efficacy of sildenafil (Revatio) has not been evaluated in patients currently on bosentan (Tracleer).

Overview

Pulmonary arterial hypertension (PAH) formerly known as primary pulmonary hypertension (PPH) is characterized by elevations in pulmonary arterial pressure to greater than 25 mm Hg at rest and greater than 30 mm Hg with exercise.^{4,5} Symptoms include dyspnea, fatigue, chest pain, palpitations, syncope, and edema. Prognosis varies based on severity of disease, whether right heart failure is present, and response to vasodilator therapy.

Oral calcium channel blockers are used in patients who exhibit acute vasoreactivity.⁶ FDA approved treatments for PAH include prostacyclin and prostacyclin analogs [epoprostenol (Prostacyclin®), terprostiniil (Remodulin®), iloprost (Ventavis®)], and endothelin receptor antagonists [bosentan (Tracleer) and ambrisentan (Letairis)] and sildenafil (Revatio).⁷ In addition to calcium channel blockers, bosentan (Tracleer), ambrisentan (Letairis) and sildenafil (Revatio) are oral treatment options. The only phosphodiesterase 5 inhibitor FDA approved for the treatment of PAH is sildenafil (Revatio). Sildenafil (Viagra®) is also FDA-approved for erectile dysfunction. This review will focus on oral medications only: ambrisentan (Letairis), bosentan (Tracleer) and sildenafil (Revatio).

The stages of PAH disease have been classified by the World Health Organization (WHO). The classifications are based on the effect of the disease on the patient's ability to function (class I: no limitation of physical activity; class II: mild limitation of physical activity; class III: marked limitation of physical activity; class IV: inability to perform any physical activity).⁸ The WHO classification also takes into account the presence or absence of syncope.

According to the 2007 update to the evidence-based American College of Chest Physicians (ACCP) guidelines, only patients who demonstrate acute vasoreactivity should be considered for

calcium channel blocker therapy (Grade B).⁹ The risks and benefits of treatment in early PAH should be considered carefully. Patients not candidates for calcium channel blocker therapy may consider other alternative oral therapies depending upon their Functional Class (FC) grouping. For FC II, the phosphodiesterase inhibitor sildenafil is an option (Grade A). First line oral therapy for FC III includes the endothelin antagonist bosentan (Grade A) or the phosphodiesterase inhibitor sildenafil (Grade A). The inhaled and injectable prostanoids including epoprostenol (Grade A), treprostinil (Grade B), and iloprost (Grade A) are also considered as therapeutic options for treatment of FC III and FC IV. Oral options for FC IV include bosentan (Grade B) and sildenafil (Grade C). Ambrisentan was still investigational at the time of publication of this updated guideline.

Pharmacology^{10,11,12}

Endothelin-1 (ET-1) is a neurohormone whose effects are mediated by binding to receptors in the endothelium and vascular smooth muscle. Increased ET-1 concentrations in the plasma and lung tissue occur in patients with PAH. Two receptor subtypes, ET_A and ET_B mediate the effects of ET-1 in the vascular smooth muscle and endothelium. Bosentan (Tracleer), a competitive antagonist at the endothelin receptor (ET_A and ET_B), was the first in this new drug class known as endothelin (ET-1) receptor antagonists. The newest agent in this class, ambrisentan (Letairis), is selective at the ET_A receptor.

Sildenafil (Revatio) inhibits phosphodiesterase type five (PDE-5) in smooth muscle of pulmonary vasculature where PDE-5 is responsible for the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation; vasodilation in the pulmonary bed and the systemic circulation (to a lesser degree) can occur.

Pharmacokinetics

Drug	Half-life (hr)	Bioavailability (%)	Metabolite	Excretion (%)
ambrisentan (Letairis) ¹³	9	Unknown	Unknown	Renal: minor Non-Renal: major
bosentan (Tracleer) ¹⁴	5	50	Two inactive and one active that contributes 10 ~ 20 percent of parent drug activity	Renal: 3 Feces: 97
sildenafil (Revatio) ¹⁵	4 (for parent drug and metabolite)	40	N-desmethyl metabolite (active with in vitro potency of PDE-5 ~ 50 percent of parent drug)	Renal: 13 Feces: 80

Ambrisentan (Letairis) is a substrate of P glycoprotein (P gp) and is 99 percent protein bound.

Bosentan (Tracleer) is an inducer of CYP450 2C9 and 3A4 and possibly 2C19.

Sildenafil (Revatio) is metabolized through the CYP450 3A4 (major) and 2C9 (minor) isoenzyme systems.

Contraindications/Warnings^{16,17,18}

Ambrisentan (Letairis) has two black box warnings related to potentially serious liver injury and likelihood of serious birth defects if used by pregnant women. Elevation of liver transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] to at least three times the upper limit of normal (ULN) have occurred with the use of ambrisentan in 0.8 percent of patients in 12-week trials and 2.8 percent of patients including long-term open-label trials up to one year. Elevations in aminotransferases require close attention. Additionally, ambrisentan is very likely to produce serious birth defects if used by pregnant women. Due to the risks of liver damage and birth defects, ambrisentan is available only through a special restricted distribution program for pharmacies, prescribers and patients known as LEAP (Letairis Education and Access Program).

Bosentan (Tracleer) has black box warning related to potentially serious liver injury. Rare cases of unexplained hepatic cirrhosis have been reported after prolonged use (>12 months) of bosentan in patients with multiple co-morbidities drug therapies. There have also been rare reports of liver failure. Strict adherence to the monthly monitoring schedule for the duration of treatment is required to use bosentan. Also, due to the significant potential for fetal harm as well as the potential for serious liver damage, bosentan (Tracleer) can only be accessed through the Tracleer Access Program by calling 1-866-228-3546.

Concurrent administration with organic nitrates (nitroglycerin) or in any form with sildenafil (Revatio) is contraindicated as the combination potentiates the hypotensive effects.

Adverse Effects

Drug	Epistaxis	Head-ache	Dyspepsia	Flushing	Insomnia	Erythema	Elevations in ALT/AST (> 3X ULN)
ambrisentan (Letairis) ¹⁹	nr	15 (14)	nr	4 (1)	nr	nr	0.8-2.8
bosentan (Tracleer) ²⁰	nr	22 (20)	4 (0)	9 (5)	nr	nr	11 (2)
sildenafil 20 mg three times daily (Revatio) ²¹ n=69 (placebo n=70)	9 (1)	46 (39)	13 (7)	10 (4)	7 (1)	6 (1)	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

In post marketing experience, there have been cases of sudden decrease or loss of hearing in temporal association with the use of PDE5 inhibitors like sildenafil (Revatio). It is not possible to

determine whether these reported events are directly related to the use of the drug, to the patient's underlying risk factors, to a combination of these, or to other factors.²²

Special Populations^{23,24,25}

Pediatrics

Safety and efficacy of ambrisentan (Letairis), bosentan (Tracleer) or sildenafil (Revatio) have not been established in pediatric pulmonary hypertension patients.

Pregnancy

Ambrisentan (Letairis) and bosentan (Tracleer) are categorized as Pregnancy Category X and are expected to cause fetal harm if administered to pregnant women. Pregnancy must be excluded before initiating therapy with either of these products and prevented thereafter using reliable methods of birth control.

Sildenafil (Revatio) is categorized as Pregnancy Category B; there are no adequate and well-controlled studies in pregnant women.

Dosages

Drug	Initial Dose	Maximum Daily Dose	How Supplied
ambrisentan (Letairis) ²⁶	5 mg once daily with or without food	10 mg once daily	5, 10 mg tablets
bosentan (Tracleer) ²⁷	62.5 mg twice daily for first four weeks	125 mg twice daily	62.5, 125 mg tablets
sildenafil (Revatio) ²⁸	20 mg three times daily	20 mg three times daily	20 mg tablet

No dosage adjustments are recommended for ambrisentan (Letairis) in mild to moderate renal impairment. Ambrisentan (Letairis) is not recommended in patients with moderate to severe hepatic impairment.

No dosage adjustments are recommended for sildenafil (Revatio) in renal or hepatic impairment in patients with PAH.

Bosentan (Tracleer) should be avoided in patients with PAH who have moderate to severe hepatic impairment (see Black Box Warning and dosage adjustment and monitoring instructions in the package insert).

Clinical Trials

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by the manufacturer. Search strategy included the use of ambrisentan, bosentan and sildenafil for FDA-approved indication for PAH. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent

with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

sildenafil (Revatio) and placebo

In a randomized, double-blind, placebo-controlled study, 278 patients (277 randomized, one patient not treated) with symptomatic PAH received placebo or sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks.²⁹ The primary endpoint of distance walked in six minutes which increased 45 m (+13 percent), 46 m (+13.3 percent), and 50 m (+14.7 percent) for 20, 40, and 80 mg sildenafil groups, respectively (p=0.001). There was no change in the placebo group. Mean pulmonary artery pressure, World Health Organization (WHO) functional class and the incidence of clinical worsening were also assessed, but the study was not powered to assess mortality. Mean pulmonary artery pressure decreased 2.1, 2.6, and 4.7 mm Hg in the 20, 40, 80 mg sildenafil groups, respectively, compared to an increase of 0.6 mm Hg in placebo. The WHO functional class was improved in the sildenafil groups. The incidence of clinical worsening did not differ significantly between sildenafil and placebo. Common adverse events included flushing, dyspepsia, and diarrhea in the treatment arm. A total of 222 patients entered a long-term extension study of sildenafil monotherapy and showed a 51 m increase in distance walked in six minutes at one year. Study doses exceed FDA labeled doses.

Improvements in exercise tolerance, cardiac index, and QOL were demonstrated in a randomized, double-blind, placebo-controlled, crossover design trial. The evaluation compared the efficacy of sildenafil 25 to 100 mg three times daily to placebo in patients with primary pulmonary hypertension (PPH) over 12 weeks.³⁰ The primary endpoint was the change in exercise time on treadmill using the Naughton protocol (a graded exercise evaluation treadmill stress test).³¹ Exercise time increased by 44 percent from 475 ± 168 seconds at the end of placebo phase to 686 ± 224 seconds at the end of sildenafil phase (p=0.0001). Secondary endpoints of cardiac index improved from 2.80 ± 0.9 L/m² to 3.45 ± 1.1 L/m² (p=0.0001), whereas pulmonary artery systolic pressure decreased insignificantly from 105.23 ± 17.82 mm Hg to 98.50 ± 24.38 mm Hg. There was significant improvement in the dyspnea and fatigue components of the QOL questionnaire. During the placebo phase, one patient died, and another had syncope. There were no significant side effects with sildenafil.

sildenafil (Revatio) and bosentan (Tracleer)

In a double-blind trial, 26 patients with PAH (WHO functional class III) were randomized to receive sildenafil 50 mg twice daily for four weeks then 50 mg three times daily or bosentan 62.5 mg twice daily for four weeks then 125 mg twice daily over 16 weeks. Intention-to-treat analysis showed no significant differences between the two treatment groups as both improved right ventricular (RV) mass, six-minute walk distance, and cardiac index.³² Study doses of sildenafil exceed FDA labeled doses.

bosentan (Tracleer) and placebo

The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was a 16-week, multicenter, randomized, double-blind, placebo-controlled study evaluating the effect of

bosentan, a dual endothelin receptor antagonist, on systemic pulse oximetry (primary safety end point) and pulmonary vascular resistance (primary efficacy end point) in patients with World Health Organization functional class III Eisenmenger syndrome. Hemodynamics were assessed by right- and left-heart catheterization.³³ Eisenmenger syndrome is characterized by the development of pulmonary arterial hypertension with consequent intracardiac right-to-left shunt and hypoxemia in patients with preexisting congenital heart disease. Secondary end points included exercise capacity assessed by six-minute walk distance, additional hemodynamic parameters, functional capacity, and safety. Fifty-four patients were randomized 2:1 to bosentan (n=37) or placebo (n=17) for 16 weeks. The placebo-corrected effect on systemic pulse oximetry was one percent (95% confidence interval, -0.7 to 2.8), demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced pulmonary vascular resistance index (-472.0 dyne.s.cm⁻⁵; p=0.0383). The mean pulmonary arterial pressure decreased (-5.5 mm Hg; p=0.0363), and the exercise capacity increased (53.1 m; p=0.0079). Four patients discontinued as a result of adverse events, two (five percent) in the bosentan group and two (12 percent) in the placebo group. Bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation.

The purpose of the study was to investigate the effects of bosentan (125 or 250 mg twice daily) on echocardiographic and Doppler variables in 85 patients with World Health Organization class III or IV PAH.³⁴ Patients had primary pulmonary hypertension (84 percent) or PAH associated with connective tissue disease. Of these, 29 patients received placebo and 56 received bosentan (1:2 randomization). Six-minute walk tests and echocardiograms were performed at baseline and after 16 weeks of treatment. Baseline characteristics were similar in the placebo and bosentan groups, and echocardiographic and Doppler findings were consistent with marked abnormalities of right ventricular (RV) and left ventricular (LV) structure and function that were due to PAH. The treatment effect on six-minute walking distance was 37 m in favor of bosentan (p=0.036). Treatment effects of bosentan compared with placebo on other parameters were statistically significant. Bosentan improved RV systolic function and LV early diastolic filling and lead to a decrease in RV dilation and an increase in LV size in patients with PAH.

The EARLY trial was a multi-center, double-blind, randomized, placebo-controlled trial of 185 patients with WHO class II PAH to assess the effectiveness of bosentan (n=93) versus placebo (n=92).³⁵ The primary endpoints were pulmonary vascular resistance at month six expressed as a percentage of baseline and change from baseline in six minute walk distance. Analyses were completed for 168 patients (n=80 for bosentan group; n=88 for placebo group). The average six minute walk distance increased from baseline in the bosentan group by 11.2 m and decreased in the placebo group by 7.9 m (p=0.0758). Serious adverse events (e.g. syncope, right ventricular failure) were reported in 12 of the patients in the bosentan group and eight in the placebo group. The findings suggest that there may be a beneficial use for bosentan in patients with WHO class II PAH. This study was funded by the manufacturer of bosentan. Bosentan is not currently FDA-approved for patients with WHO class II PAH, however the manufacturer has submitted the data for review for this patient population.

ambrisentan (Letairis) and placebo

ARIES-1 and ARIES-2 were two 12-week, randomized, double-blind, placebo-controlled, multicenter studies conducted in 393 patients with PAH (WHO Group I).^{36,37} The study designs were identical with the exception of the comparative doses used (ARIES-1: ambrisentan 5 mg and 10 mg; ARIES-2: ambrisentan 2.5 mg and 5 mg) and the geographic locations. Both studies allowed the addition of ambrisentan or placebo to current therapy except epoprostenol,

treprostinil, iloprost, bosentan or sildenafil. The primary study endpoint was the six minute walk distance. Both studies showed that active treatment with ambrisentan resulted in significant improvement in six minute walk distance and improvements increased with dose ($p < 0.001$). Additionally, time to clinical worsening was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents or study withdrawal due to early escape. Early escape is defined as any two of the following: a 20 percent decrease in the six minute walk distance; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. There was a significant delay in the time to clinical worsening for patients receiving ambrisentan versus placebo (ARIES-1: 97 versus 89 percent; $p = 0.030$ and ARIES-2: 94 versus 79 percent; $p = 0.005$).

bosentan (Tracleer) and ambrisentan (Letairis)

Due to a lack of other data on survival for agents in this class, this analysis has been included. A retrospective cohort analysis was conducted from two double-blind, randomized trials and their open-label extensions, treated with first-line bosentan, with a three year follow-up.³⁸ The results suggest that first-line bosentan therapy followed by the addition of other disease-specific therapies as required, improves survival in patients with advanced PAH. Some uncontrolled observational studies suggest ambrisentan may be a once-daily alternative for patients who have experienced asymptomatic aminotransferase elevations on other endothelin receptor antagonists after aminotransferase levels have returned to normal.

Summary

The treatment for PAH is challenging and complicated. Untreated PAH is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular failure and death.

Sildenafil (Revatio) is the only PDE-5 inhibitor FDA approved for PAH. Sildenafil (Revatio) has been found to be effective in reducing right ventricular (RV) mass, mean pulmonary artery pressure, and improving exercise tolerance.^{39,40,41}

The endothelin receptor antagonists, bosentan (Tracleer) and ambrisentan (Letairis), have been shown to improve exercise capacity, hemodynamics, quality of life and increase time to clinical worsening in short-term studies.

The current studies with sildenafil (Revatio) and ambrisentan (Letairis) are few, small and of short duration and so the place in therapy may yet evolve for these two agents.

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