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Therapeutic Class Review
Pulmonary Arterial Hypertension Agents

Overview/Summary

All medications included in this review are Food and Drug Administration (FDA)-approved for the treatment of pulmonary arterial hypertension (PAH).¹⁻⁹ The differences in the sub-populations in their indications are due to the specific study groups in the trials on which FDA-approval was based. Sildenafil and tadalafil are also indicated for erectile dysfunction under different trade names; however, this indication will not be discussed in this review. Only epoprostenol is currently available as a generic formulation.¹⁰

PAH is characterized by elevated pulmonary arterial pressure and increased pulmonary vascular resistance leading to right heart failure. The prevalence of PAH is estimated to be 15 cases/one million adults. The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy.¹¹ The World Health Organization (WHO) classifies pulmonary hypertension into five groups. WHO Group 1 encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorders, portal hypertension, human immunodeficiency virus infection, drugs and toxins and other disorders that affect the small pulmonary muscular arterioles.¹² Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.¹¹

There are three classes of medications that are FDA-approved for the treatment of WHO Group 1 PAH: prostanoids, endothelin receptor antagonists (ERAs) and phosphodiesterase (PDE)-5 inhibitors. In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I₂, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation.¹¹ The prostanoids, epoprostenol, iloprost and treprostinil, act as vasodilators and platelet aggregation inhibitors.²⁻⁴ Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction which is mediated by the endothelin receptors, ET_A and ET_B.^{6,11} Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance.⁶ The ERAs, ambrisentan and bosentan, competitively bind to both receptors with different affinities. Ambrisentan is highly selective for the ET_A receptor, while bosentan is only slightly more selective for the ET_A receptor than the ET_B receptor. However, the clinical significance of receptor affinities of the ERAs is unknown.^{6,7} PAH is also associated with impaired release of nitric oxide by the vascular endothelium resulting in reduction of cyclic guanosine monophosphate (cGMP) concentrations. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.¹¹ The PDE5 inhibitors, sildenafil and tadalafil, increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.^{8,9}

National and international consensus guidelines recommend oral therapy with either an ERA or a PDE5 inhibitor as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.^{11,13,14} Intravenous therapy with epoprostenol or treprostinil should be initiated as first line in patients at higher risk and poor prognostic indexes. Epoprostenol is the preferred treatment for the most severely ill patients and is the only therapy shown to prolong survival.¹¹ At the time the treatment guidelines were published, inhaled treprostinil and oral tadalafil were not FDA-approved for the treatment of PAH.

Medications

Table 1. Medications Included Within Class Review¹⁻⁹

Generic Name (Trade name)	Medication Class	Generic Availability
Ambrisentan (Letairis [®])	Endothelin receptor antagonist	-
Bosentan (Tracleer [®])	Endothelin receptor antagonist	-
Epoprostenol (Flolan ^{®*} , Veletri ^{®†})	Prostanoid	✓
Iloprost (Ventavis [®])	Prostanoid	-
Sildenafil (Revatio [®])	Phosphodiesterase inhibitor	-
Tadalafil (Adcirca [®])	Phosphodiesterase inhibitor	-
Treprostinil inhalation solution (Tyvaso [®])	Prostanoid	-
Treprostinil sodium injection (Remodulin [®])	Prostanoid	-

*Available generically in one dosage form or strength.

†Unlike Flolan[®], which has to be discarded after eight hours (non-refrigerated) or 48 hours (refrigerated), Veletri[®] is stable for 24 hours (non-refrigerated) and five days (refrigerated).

Indications

Table 2. Food and Drug Administration Approved Indications¹⁻⁹

Indication	Ambrisentan	Bosentan	Epoprostenol	Iloprost	Sildenafil	Tadalafil	Treprostinil
Treatment of PAH (WHO Group I) in patients with WHO class II or III symptoms to improve exercise ability and delay clinical worsening	✓						
Treatment of PAH (WHO Group I) in patients with NYHA class II to IV symptoms to improve exercise ability and decrease clinical worsening		✓					
Long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA class III and class IV patients who do not respond adequately to conventional therapy			✓				
Treatment of PAH (WHO Group I) in patients with NYHA class III or IV symptoms				✓			
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening					✓ *		
Treatment of PAH (WHO Group I) to improve exercise ability						✓ †	
Treatment of PAH (WHO Group I) in patients with NYHA class III symptoms, to improve exercise ability							✓ (inhalation solution [‡])
Treatment of PAH (WHO Group I) to diminish symptoms associated with exercise and to reduce the rate of clinical deterioration in patients who require transition from epoprostenol							✓ (sodium injection [§])

NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization

* Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

† Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

‡ Studies included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

§ Studies included patients with NYHA class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).

Pharmacokinetics**Table 3. Pharmacokinetics**^{1-9,15}

Generic Name	Bioavailability (%)	Time to Peak Plasma Concentration	Excretion (%)	Metabolism (active metabolites)	Serum Half-Life (hours)
Ambrisentan	Unknown; not affected by food	2 hours	Primarily non-renal; relative contributions not well established	Hepatic: CYP3A, CYP2C19; UGT-1A9S, 2B7S, and 1A3S (4-hydroxymethyl ambrisentan)	9
Bosentan	50; not affected by food	3 to 5 hours	Biliary; urine (<3)	Hepatic: CYP3A, CYP2C9 (Ro 48-5033)	5
Epoprostenol	Not reported	Not reported	Feces (4); urine (82)	Blood: rapid hydrolysis, enzymatic and non-enzymatic degradation (6-keto-PGF _{1α} , 6,15-diketo-13,14-dihydro-PGF _{1α})	6 minutes
Iloprost	Not reported	Not reported	Feces (12); urine (68)	Hepatic: β-oxidation (major), CYP450 (minor) (tetranor-iloprost)	20 to 30 minutes
Sildenafil	41; high fat meal decreases absorption	30 to 120 minutes (median, 60 minutes)	Feces (80); urine (13)	Hepatic: CYP3A4 (major) and CYP2C9 (minor) (N-desmethyl metabolite)	4
Tadalafil	Not reported; not affected by food	2 to 8 hours (median, 4 hours)	Feces (61); urine (36)	Hepatic: CYP3A4 (none)	15 (healthy); 35 (pulmonary hypertension, not on bosentan)
Treprostinil inhalation solution	64 (18 µg); 72 (36 µg)	0.25 and 0.12 hours	Feces (13); urine (79; 4 unchanged)	Hepatic: CYP2C8 (none)	4
Treprostinil sodium injection	100	Not reported	Feces (13); urine (79, 4 unchanged, 64 metabolites)	Hepatic: CYP2C8 (none)	4

UGT=uridine 5'-diphosphate glucuronosyltransferases

Clinical Trials

The efficacy and safety of ambrisentan in the treatment of pulmonary arterial hypertension (PAH) was established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared ambrisentan to placebo in a total of 394 patients. Compared to placebo, treatment with ambrisentan resulted in a significant increase in exercise capacity as measured by the 6-minute walk distance (6MWD).¹⁶ ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After one year of treatment, there was an improvement in 6MWD in the 2.5, 5, and 10 mg ambrisentan groups (25, 28, and 37 m, respectively). After two years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m).¹⁷

Bosentan was originally Food and Drug Administration (FDA)-approved in PAH patients with World Health Organization (WHO) functional class III and IV symptoms based on the results from two randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all bosentan groups compared to placebo. Bosentan was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO functional class symptoms.¹⁸⁻¹⁹ The FDA-approved indication was subsequently expanded to include patients with WHO functional class II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with bosentan resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening function class symptoms in the bosentan group compared to placebo.²⁰

Epoprostenol was evaluated in three randomized, open-label studies comparing epoprostenol plus conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or oxygen supplementation) to conventional therapy alone. In an eight-week trial by Rubin et al consisting of 24 patients with idiopathic PAH, treatment with epoprostenol plus conventional therapy resulted in significant improvement in 6MWD and hemodynamic values compared to baseline, but the magnitude of differences between the groups was not statistically significant.²¹ In the other two 12-week trials by Barst et al and Badesch et al consisting of 81 and 111 patients with WHO functional class III or IV PAH, respectively, significant differences in 6MWD and hemodynamic values were observed with epoprostenol plus conventional therapy compared to conventional therapy alone.^{22,23}

The FDA-approval of iloprost was based on a randomized, double-blind, placebo-controlled trial of 203 patients with New York Heart Association (NYHA) class III or IV PAH. The primary efficacy endpoint was clinical response defined as a composite of improvement in 6MWD of 10%, improvement by at least one NYHA class, and no death or deterioration of pulmonary hypertension. After 12 weeks, the combined endpoint was met by 16.8% of the patients receiving iloprost, as compared with 4.9% of the patients receiving placebo ($P=0.007$).²⁴

The efficacy and safety of sildenafil was evaluated in the SUPER study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO functional class II or III symptoms. Compared to placebo, sildenafil significantly improved exercise capacity, as measured by the 6MWD, WHO functional class symptoms and hemodynamics.²⁵ The addition of sildenafil to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO functional class II or III symptoms. Sildenafil added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo.²⁶

Tadalafil was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO functional class II or III symptoms. Treatment with tadalafil significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo.²⁷

The FDA-approval of treprostinil solution for inhalation was based on the results of the TRIUMPH-1 trial, a randomized, double-blind, placebo-controlled study consisting of 235 patients. Nearly all patients had NYHA class III symptoms and all were receiving either bosentan or sildenafil for at least three months prior to study initiation. After 12 weeks of treatment, there was a significant increase in the 6MWD in the treprostinil group compared to placebo.²⁸

Treprostinil sodium for injection was evaluated in a 12-week, multicenter, randomized, double-blind, placebo-controlled trial in which subcutaneous infusion of treprostinil sodium was compared to placebo in 470 patients with predominantly NYHA class III symptoms. Treatment with treprostinil sodium resulted in the between group median increase of 16 m in the 6MWD compared to placebo ($P=0.006$).²⁹

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Galie et al¹⁶ (ARIES-1)</p> <p>Ambrisentan 5 or 10 mg daily</p> <p>vs</p> <p>placebo</p> <p>and</p> <p>(ARIES-2)</p> <p>Ambrisentan 2.5 or 5 mg daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT (1:1:1)</p> <p>Patients (mean ages 44 to 53 years) with PAH, idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use</p>	<p>ARIES-1 N=202</p> <p>ARIES-2 N=192</p> <p>12 weeks</p>	<p>Primary: Change from baseline in exercise capacity measured by 6MWD</p> <p>Secondary: Time to clinical worsening, change in WHO functional class, SF-36 Health Survey score, Borg dyspnea score, and plasma B-type natriuretic peptide concentration</p>	<p>Primary: There was a significant increase in 6MWD in all ambrisentan groups compared to placebo. The mean placebo-corrected 6MWD in ARIES-1 was 31 m (95% CI, 3 to 59; $P=0.008$) for ambrisentan 5 mg and 51 m (95% CI, 27 to 76; $P<0.001$) for ambrisentan 10 mg. In ARIES-2, the placebo-corrected 6MWD was 32 m (95% CI, 2 to 63; $P=0.022$) for ambrisentan 2.5 mg and 59 m (95% CI, 30 to 89; $P<0.001$) for ambrisentan 5 mg.</p> <p>Secondary: In ARIES-1, there was improvement in time to clinical worsening; however, it was not statistically significant compared to placebo in the 5, 10, and 5 and 10 mg combined groups ($P=0.307$, $P=0.292$, $P=0.214$, respectively). In ARIES-2, there was a significant improvement in time to clinical worsening in the 2.5, 5, and 2.5 and 5 mg combined groups compared to placebo ($P=0.005$, $P=0.008$, $P<0.001$, respectively).</p> <p>In ARIES-1, the distribution of WHO functional class significantly improved in the ambrisentan group compared to placebo ($P=0.036$). In ARIES-2, the distribution of WHO functional class in the ambrisentan group improved, but it was not statistically significant vs placebo ($P=0.117$).</p> <p>In ARIES-1, there was an improvement in SF-36 scales, but it was not statistically significant compared to placebo (P value not reported). In ARIES-2, SF-36 scales significantly improved in the combined ambrisentan group compared to placebo ($P=0.005$).</p> <p>There was a significant improvement in Borg dyspnea scores in the combined ambrisentan groups compared to placebo in ARIES-1 (-0.6; 95% CI, -1.2 to 0.0; $P=0.017$) and ARIES-2 (-1.1; 95% CI, -1.8 to -0.4; $P=0.019$). There were also significant improvements in Borg dyspnea scores compared to placebo for the 10 mg ambrisentan group in ARIES-1 (-0.9; 95% CI, -1.6 to -0.2; $P=0.002$), and for the 2.5 (-1.0; 95% CI, -1.9 to -0.2; $P=0.046$) and 5 mg (-1.2; 95% CI, -2.0 to -0.4; $P=0.040$) groups in ARIES-2.</p> <p>There was a significant decrease in plasma B-type natriuretic peptide concentrations compared to placebo in the 5 and 10 mg groups in ARIES-1 and</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>the 2.5 and 5 mg groups in ARIES-2 ($P < 0.003$ in all groups).</p> <p>Most of the adverse events were either mild to moderate and included peripheral edema, headache and nasal congestion. The proportion of patients who discontinued treatment due to adverse events was 3.0% in the placebo groups and 2.3% in the ambrisentan groups.</p>
<p>Oudiz et al¹⁷ (ARIES-E)</p> <p>Ambrisentan 2.5, 5, or 10 mg daily</p>	<p>ES, MC, OL</p> <p>Patients (mean ages 49 to 52 years) with PAH that completed ARIES-1 and ARIES-2</p>	<p>N=350</p> <p>Ongoing</p>	<p>Primary: Change from baseline in exercise capacity measured by 6MWD, Borg dyspnea score, WHO functional class, long-term survival, and time to clinical worsening</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>After one year of treatment there was an improvement in 6MWD of 25 m (95% CI, 5 to 45) for the 2.5 mg group, 28 m (95% CI, 14 to 42) for the 5 mg group, and 37 m (95% CI, 22 to 52) for the 10 mg group. After two years of treatment, improvements were sustained in the 5 (23 m; 95% CI, 9 to 38) and 10 mg (28 m; 95% CI, 11 to 45) groups, but not the 2.5 mg group (7 m; CI, -13 to 27).</p> <p>After one year of treatment, there were improvements in Borg dyspnea scores for the 5 (-0.59; 95% CI, -0.94 to -0.23) and 10 mg (-5.1; 95% CI, -1.00 to -0.03) groups, but not the 2.5 mg group (-0.08; 95% CI, -0.55 to 0.38). The trend continued after two years of treatments with changes in Borg dyspnea scores from baseline of -0.33 (95% CI, -0.68 to 0.03) for the 5 mg, -0.60 (95% CI, -1.08 to -0.11) for the 10 mg, and 0.23 (95% CI, -0.31 to 0.76) for the 2.5 mg groups.</p> <p>WHO functional class was either improved or maintained in 79 to 89% of patients.</p> <p>The survival estimate for the overall population was 94% (95% CI, 91 to 96) at one year and 88% (95% CI, 83 to 91) at two years.</p> <p>After one year, 83% (95% CI, 79 to 87) of the overall population was free from clinical worsening and 72% (95% CI, 67 to 76) were free from clinical worsening after two years.</p> <p>Adverse events in this study were similar to those seen in ARIES-1 and ARIES-2 and were mild to moderate consisting of peripheral edema, headache, dizziness and upper respiratory tract infection.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Channick et al¹⁸</p> <p>Bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT (2:1)</p> <p>Patients (mean ages 47 to 52 years) with symptomatic, severe primary pulmonary hypertension or pulmonary hypertension due to scleroderma (WHO functional class III to IV), despite previous treatment with vasodilators, anticoagulants, diuretics, cardiac glycosides, or supplemental oxygen</p>	<p>N=32</p> <p>12 weeks</p>	<p>Primary: Exercise capacity measured by 6MWD</p> <p>Secondary: Changes from baseline in cardiopulmonary hemodynamics, Borg dyspnea index, WHO functional class, and withdrawal due to clinical worsening</p>	<p>Primary: At week 12, the 6MWD significantly increased from baseline in the bosentan group by 70 m ($P<0.05$) and decreased in the placebo group by 6 m (P value not reported). The mean change in 6MWD was 76 m (95% CI, 12 to 139; $P=0.021$) further for the bosentan group compared to the placebo group.</p> <p>Secondary: At week 12, the bosentan group had significantly improved cardiopulmonary hemodynamics compared to the placebo group. Pulmonary vascular resistance, mean pulmonary artery pressure, pulmonary capillary wedge pressure and mean right arterial pressure all significantly decreased compared to placebo with mean differences of -415 dynes·s/cm⁵ (95% CI, -608 to -221; $P<0.0002$), -6.7 mm Hg (95% CI, -11.9 to -1.5; $P=0.013$), -3.8 mm Hg (95% CI, -7.3 to -0.3; $P=0.035$) and -6.2 (95% CI, -9.6 to -2.7; $P=0.001$), respectively. Cardiac index was significantly greater in the bosentan group compared to the placebo group with a mean difference of 1.0 L/min/m² (95% CI, 0.6 to 1.4; $P<0.0001$).</p> <p>At week 12, the Borg dyspnea index was 1.6 (95% CI, 0.0 to 3.1; P value not reported) lower in the bosentan group compared to the placebo group.</p> <p>At baseline, all patients in the study population were in WHO functional class III. After 12 weeks of therapy, 43% of patients improved to WHO functional class II and 57% of patients remained in WHO functional class III in the bosentan group ($P=0.0039$). In the placebo group, 9% of patients improved to WHO functional class II, 73% remained in WHO functional class III and 18% worsened to WHO functional class IV ($P=1.0000$). Overall, bosentan significantly improved WHO functional class compared to placebo ($P=0.019$).</p> <p>The time to clinical worsening was significantly increased in the bosentan group compared to the placebo group ($P=0.033$) with three withdrawals in the placebo group and none in the bosentan group.</p> <p>Adverse events in both the placebo and bosentan groups were similar with the exception of an asymptomatic increase in hepatic aminotransferases in two patients in the bosentan group which returned to normal without discontinuation of the study drug.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Rubin et al¹⁹ (BREATHE-1)</p> <p>Bosentan 62.5 mg twice daily for 4 weeks, then 125 or 250 mg twice daily for 12 weeks</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT</p> <p>Patients (mean ages 47 to 50 years) with symptomatic, severe primary pulmonary hypertension or pulmonary hypertension due to connective-tissue disease (WHO functional class III or IV) despite treatment with anticoagulants vasodilators, diuretics, cardiac glycosides, or supplemental oxygen</p>	<p>N=213</p> <p>16 weeks</p>	<p>Primary: Change from baseline in exercise capacity measured by 6MWD</p> <p>Secondary: Changes from baseline in Borg dyspnea index, WHO functional class, and the time to clinical worsening</p>	<p>Primary: After 16 weeks, there was an increase in 6MWD of 36 m in the combined bosentan groups compared to a decrease of 8 m in the placebo group for a mean difference of 44 m (95% CI, 21 to 67; <i>P</i><0.001).</p> <p>Secondary: After 16 weeks, the Borg dyspnea index decreased by a mean of -0.1 ± 0.2 in the 125 mg group and -0.6 ± 0.2 in the 250 mg group compared to a mean increase of 0.3 ± 0.2 in the placebo group. The mean treatment effect favored bosentan by -0.6 (95% CI, -1.2 to -0.1). The placebo-corrected improvement was greater for the 250 mg group (-0.9; <i>P</i>=0.012) compared to the 125 mg group (-0.4; <i>P</i>=0.42).</p> <p>At week 16, 38% of patients in the 125 mg group, 34% of patients in the 250 mg group, and 28% of patients in the placebo group had improved to WHO functional class II, while 3% of patients in the 125 mg group, 1% of patients in the 250 mg group and 0% of patients in placebo group had improved to WHO functional class I. Overall, there was a mean treatment effect of 12% favoring bosentan (95% CI, -3 to 25).</p> <p>After 16 weeks, bosentan significantly increased the time to clinical worsening compared to placebo (<i>P</i>=0.004).</p>
<p>Galie et al²⁰ (EARLY)</p> <p>Bosentan 62.5 mg twice daily for 4 weeks, then 125 mg twice daily (or 62.5 mg twice daily if weight <40 kg)</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, PG, RCT (1:1)</p> <p>Patients ≥ 12 years of age with WHO functional class II idiopathic PAH, familial PAH, or PAH associated with HIV infection, anorexigen use, atrial septal</p>	<p>N=185</p> <p>6 months</p>	<p>Primary: Change from baseline in pulmonary vascular resistance and 6MWD</p> <p>Secondary: Time to clinical worsening and change from baseline in WHO</p>	<p>Primary: At six months, the bosentan group had a mean pulmonary vascular resistance 83.2% (95% CI, 73.8 to 93.7) of the baseline value compared to 107.5% (95% CI, 97.6 to 118.4) of the baseline value in the placebo group for a treatment effect of -22.6% (95% CI, -33.5 to -10.0; <i>P</i><0.0001) favoring bosentan.</p> <p>At six months, the mean 6MWD increased in the bosentan group by 11.2 m (95% CI, -4.6 to 27.0) and decreased in the placebo group by 7.9 m (95% CI, -24.3 to 8.5). The treatment effect of 19.1 (95% CI, -3.6 to 41.8; <i>P</i>=0.0758) favored bosentan, yet was not statistically significant.</p> <p>Secondary: There was a significant delay in time to clinical worsening with the bosentan</p>

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	defect <2 cm in diameter, ventricular septal defect <1 cm in diameter, patent ductus arteriosus, or connective tissue or auto-immune diseases		functional class, Borg dyspnea index, total pulmonary resistance, mean pulmonary arterial pressure, cardiac index, and mixed venous oxygen saturation	<p>group compared to the placebo group (HR, 0.227; 95% CI, 0.065 to 0.798; $P=0.0114$).</p> <p>At six months, there was a significantly lower incidence of worsening WHO functional class in the bosentan group compared to the placebo group (3.4 vs 13.2%; $P=0.0285$). There were no significant differences seen in Borg dyspnea index with a mean treatment effect of -0.4 (95% CI, -1.0 to 0.1; $P=0.2599$). There were no significant differences seen in right atrial pressure with a mean treatment effect of -0.6 (95% CI, -2.0 to 0.9; $P=0.662$). Pulmonary artery pressure was significantly lower in the bosentan group with a treatment effect favoring bosentan of -5.7 mm Hg (95% CI, -10.4 to -0.9; $P<0.0001$). Cardiac index and mixed venous oxygen saturation were significantly higher in the bosentan group compared to the placebo group with a mean treatment effect favoring bosentan of 0.24 L/min/m² (95% CI, 0.02 to 0.45; $P=0.025$) and 4.8% (95% CI, 1.9 to 7.6; $P=0.002$), respectively.</p> <p>Adverse events were similar in the placebo and bosentan groups. The most common adverse events in the bosentan group were nasopharyngitis and abnormal liver function tests.</p>
<p>Rubin et al²¹</p> <p>Epoprostenol 1 to 2 ng/kg/min increased by 1 to 2 ng/kg/min every 5 to 15 minutes plus conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen)</p> <p>vs</p> <p>conventional therapy alone</p>	<p>OL, PG, PRO, RCT</p> <p>Patients (age range 15 to 66 years) with primary PAH unresponsive or unable to tolerate oral vasodilators</p>	<p>N=24</p> <p>8 weeks</p>	<p>Primary: Effect of epoprostenol on pulmonary hemodynamics and exercise tolerance</p> <p>Secondary: Not reported</p>	<p>Primary:</p> <p>At eight weeks, there was a significant increase from baseline in the 6MWD ($P=0.011$) and cardiac output ($P=0.020$) as well as a significant decrease in the total pulmonary resistance ($P=0.022$) and total systemic resistance ($P=0.039$) in the epoprostenol group. In the conventional therapy group, only the change from baseline in 6MWD was significant ($P=0.022$). There were no significant differences between the groups in magnitude of changes from baseline.</p> <p>Adverse events seen in the study were not life-threatening and the most common included loose stools, jaw pain and photosensitivity.</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Barst et al²²</p> <p>Epoprostenol 4 ng/kg/min below tolerated dose initially with dose adjustments made based on signs, symptoms or adverse effects plus conventional therapy with anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen</p> <p>vs</p> <p>conventional therapy alone</p>	<p>MC, OL, PRO, RCT</p> <p>Patients (mean age 40 years) with severe primary pulmonary hypertension in NYHA functional class III or IV despite optimal treatment with anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides and supplemental oxygen</p>	<p>N=81</p> <p>12 weeks</p>	<p>Primary: Change in exercise capacity measured by 6MWD</p> <p>Secondary: Effects of epoprostenol on survival, quality of life, and hemodynamics</p>	<p>Primary: The 6MWD increased from baseline by a median of 31 m in the epoprostenol group compared to a 29 m decrease in the conventional therapy group ($P<0.002$).</p> <p>Secondary: Eight patients died in the conventional therapy group compared to none in the epoprostenol group ($P=0.003$). After adjusting for the significant differences between treatment groups in response to short-term infusion of epoprostenol, survival was significantly improved in the epoprostenol group ($P<0.001$).</p> <p>Quality of life was assessed using the Chronic Heart Failure Questionnaire, Nottingham Health Profile and Dyspnea-Fatigue Rating. There were significant improvements in the epoprostenol group in all four parts of the Chronic Heart Failure Questionnaire, in two out of six parts of the Nottingham Health Profile and the Dyspnea-Fatigue Rating ($P<0.01$).</p> <p>The NYHA functional class improved in 16 (40%) vs one (3%) patient, worsened in five (13%) vs three (10%) patients, and was unchanged in 19 (48%) vs 27 (87%) patients in the epoprostenol and control groups, respectively ($P<0.002$).</p> <p>Patients treated with epoprostenol showed significant improvement in mean pulmonary artery pressure, cardiac index and pulmonary vascular resistance with differences between treatment groups of -6.7 mm Hg (95% CI, -10.7 to -2.6), 0.5 L/min/m² (95% CI, 0.2 to 0.9), and -4.9 mm Hg/L/min (95% CI, -7.6 to -2.3), respectively (P values not reported). Compared to the control group, treatment with epoprostenol was associated with significant changes in the mean pulmonary artery pressure (-8 vs 3%; $P<0.002$) and mean pulmonary vascular resistance (-21 vs 9%; $P<0.001$).</p> <p>Minor complications were frequent and included jaw pain, diarrhea, flushing, headaches, nausea and vomiting. Serious complications were mostly related to the drug delivery system.</p>
<p>Badesch et al²³</p> <p>Epoprostenol ≤ 2 ng/kg/min initially,</p>	<p>MC, OL, RCT (1:1)</p> <p>Patients ≥ 16</p>	<p>N=111</p> <p>12 weeks</p>	<p>Primary: Exercise capacity measured by 6MWD</p>	<p>Primary: At week 12, there was an increase in the median 6MWD from 270 to 316 m in the epoprostenol group and a decrease from 240 to 192 m in the conventional therapy group. The difference in median distance walked between the groups</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>then titrated based on signs, symptoms, and adverse effects plus conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen)</p> <p>vs</p> <p>conventional therapy alone</p>	<p>years of age with moderate to severe PAH secondary to scleroderma spectrum disease</p>		<p>Secondary: Effects of epoprostenol on cardiopulmonary hemodynamics, Borg dyspnea score, Dyspnea-Fatigue Rating, NYHA functional class, and severity of Raynaud's phenomenon</p>	<p>was 108 m (95% CI, 55.2 to 180.0; $P < 0.001$).</p> <p>Secondary: There was significant improvement in pulmonary artery pressure, pulmonary vascular resistance, right atrial pressure, cardiac index, and mixed venous oxygen saturation in the epoprostenol group and there were differences between the groups of -5.97 mm Hg (95% CI, -8.98 to -2.96), -5.50 mm Hg/L/min (95% CI, -7.33 to -3.67), -2.46 mm Hg (95% CI, -4.54 to -0.39), 0.6 L/min/m² (95% CI, 0.39 to 0.81), and 4.62% (95% CI, 0.94 to 8.30), respectively.</p> <p>At week 12, there was an improvement in the Borg dyspnea and Dyspnea-Fatigue Rating in the epoprostenol group compared to worsening in the conventional therapy group with treatment effects of 2.5 (95% CI, 1.5 to 3.5) and -2.0 (95% CI, -3.0 to -2.0), respectively.</p> <p>At 12 weeks, there were 21 patients (38%) in the epoprostenol group that improved in NYHA functional class, compared to no patients in the conventional therapy group (P value not reported).</p> <p>There was a greater improvement in severity of Reynaud phenomenon over time in the epoprostenol group compared to the conventional therapy group with an area under the curve of 43.1±2.9 vs 52.3±3.2, respectively ($P=0.038$).</p> <p>The adverse events that occurred more commonly in the epoprostenol group included anorexia, nausea, diarrhea, jaw pain and depression.</p>
<p>Olschewski et al²⁴</p> <p>Iloprost 5 or 10 µg six to nine times daily</p> <p>vs</p> <p>placebo</p>	<p>MC, PC, RCT</p> <p>Patients (mean ages 51 to 52 years) with NYHA class III or IV primary or selected non-primary PAH (i.e., appetite-suppressant-associated,</p>	<p>N=203</p> <p>12 weeks</p>	<p>Primary: Clinical response as a composite of increase of at least 10% in 6MWD, improvement in NYHA functional class in the absence of deterioration in clinical condition</p>	<p>Primary: At 12 weeks, there was a significant treatment effect in favor of iloprost (OR, 3.97; 95% CI, 1.47 to 10.75; $P=0.007$). In a secondary analysis of the primary endpoint, only treatment assignment, and not demographic data or baseline characteristics, contributed significantly to the probability of response ($P=0.01$).</p> <p>Secondary: At 12 weeks, the percentage of patients with an increase of at least 10% in 6MWD was higher in the iloprost group; however, the difference was not significant ($P=0.06$). The absolute change in 6MWD was significantly higher by 36.4 m in the iloprost group compared to the placebo group ($P=0.004$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	<p>scleroderma-associated, or inoperable chronic thromboembolic PAH) despite use of conventional therapy (anticoagulants, diuretics, digitalis, calcium-channel blockers and supplemental oxygen)</p>		<p>or death</p> <p>Secondary: Changes in 6MWD, NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, the quality of life, clinical deterioration, death, and the need for transplantation</p>	<p>At 12 weeks, significantly more patients in the iloprost group had improvement in NYHA functional class compared to the placebo group ($P=0.03$). There was no significant difference between the groups in the percentage of patients with deterioration in NYHA functional class.</p> <p>At week 12, the mean Mahler Dyspnea Index score was significantly better in the iloprost group compared to the placebo group (change, 1.42 ± 2.59 vs 0.30 ± 2.45; $P<0.015$).</p> <p>After 12 weeks, significant decreases in cardiac output ($P<0.001$), systemic arterial oxygen saturation ($P<0.05$) and mixed venous oxygen saturation ($P<0.001$) as well as significant increases in pulmonary vascular resistance ($P<0.05$) and right atrial pressure were observed in the placebo group vs baseline. Prior to the first inhalation of the day, there were no significant differences from baseline in the iloprost group. However after inhalation, significant decreases in pulmonary artery pressure ($P<0.001$), pulmonary vascular resistance ($P<0.001$), systemic arterial pressure ($P<0.01$) and systemic arterial oxygen saturation ($P<0.05$) as well as significant increases in cardiac output ($P<0.001$) and pulmonary artery wedge pressure ($P<0.01$) were observed.</p> <p>The mean scores on the EuroQol visual-analogue scale improved significantly in the iloprost group (46.9 ± 15.9 to 52.8 ± 19.1) and decreased in the placebo group (48.6 ± 16.9 to 47.4 ± 21.1; $P=0.026$). The mean scores on the EuroQol health-sate scale improved in the iloprost group (0.49 ± 0.28 to 0.58 ± 0.27) and did not change in the placebo group (0.56 ± 0.29 to 0.56 ± 0.31; $P=0.11$).</p> <p>During the study one patient died in the iloprost group compared to four patients in the placebo group ($P=0.37$). In the iloprost group, 4.9% of patients met the criteria for clinical deterioration compared to 8.8% of patients in the placebo group ($P=0.41$). Overall, fewer patients died or deteriorated in the iloprost group than in the placebo group (4.9 vs 11.8%; $P=0.09$).</p> <p>The number of serious adverse events did not differ significantly between the groups. Jaw pain and flushing were more common in the iloprost group, but were mild and transient.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Galie et al²⁵ (SUPER Study)</p> <p>Sildenafil 20, 40, or 80 mg three times daily</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, RCT (1:1:1:1)</p> <p>Patients (mean ages 47 to 51 years) with symptomatic PAH (either idiopathic or associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts)</p>	<p>N=278</p> <p>12 weeks</p>	<p>Primary: Change from baseline in exercise capacity measured by 6MWD</p> <p>Secondary: Change in mean pulmonary artery pressure, Borg dyspnea scale, WHO functional class, incidence of clinical worsening, and safety</p>	<p>Primary: The 6MWD increased from baseline in all sildenafil groups with the mean placebo-corrected treatment effects of 45 (13.0%), 46 (13.3%), and 50 m (14.7%) for 20, 40, and 80 mg of sildenafil, respectively (all $P<0.001$). Among the 222 patients completing one year of treatment with sildenafil monotherapy, the improvement from baseline in the 6MWD was 51 m (95% CI, 41 to 60; P value not reported).</p> <p>Secondary: The mean pulmonary artery pressure was significantly reduced in patients receiving all sildenafil doses ($P=0.04$, $P=0.01$, and $P<0.001$ for the 20, 40, and 80 mg doses, respectively).</p> <p>The change from baseline in scores on the Borg dyspnea scale among the patients treated with sildenafil did not differ significantly from the change in patients treated with placebo.</p> <p>The WHO functional class significantly improved in all sildenafil groups. After 12 weeks of treatment, the proportion of patients with an improvement of at least one functional class were 7% for placebo, and 28, 36, and 42% for sildenafil 20, 40, and 80 mg, respectively ($P=0.003$, $P<0.001$, and $P<0.001$, respectively). The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil and those treated with placebo.</p> <p>Most adverse events were mild to moderate in intensity for all treatment groups. Headache, flushing, dyspepsia, back pain, diarrhea and limb pain were the most frequently reported adverse events.</p>
<p>Simonneau et al²⁶ (PACES)</p> <p>Sildenafil 20 mg three times daily titrated to 40 and 80 mg three times daily, as tolerated, at 4-week intervals</p>	<p>DB, MC, PC, PG, RCT (1:1)</p> <p>Patients (mean age 48 years) with PAH (idiopathic, associated anorexigen use or connective</p>	<p>N=267</p> <p>16 weeks</p>	<p>Primary: Change from baseline in 6MWD</p> <p>Secondary: Change in hemodynamic parameters, Borg dyspnea score,</p>	<p>Primary: The sildenafil group had a statistically significantly greater increase in the 6MWD than did the placebo group at week 16. The adjusted mean change at week 16 was 29.8 m for the sildenafil group and 1.0 m for the placebo group ($P<0.001$).</p> <p>Secondary: Compared to epoprostenol monotherapy, the addition of sildenafil resulted in a greater change in mean pulmonary artery pressure by -3.8 mm Hg and cardiac output by 0.9 L/minute, but no effect on Borg dyspnea score (P values not reported).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs placebo</p> <p>Patients were also receiving intravenous epoprostenol therapy.</p>	<p>tissue disease, or corrected congenital heart disease), who were receiving long-term intravenous epoprostenol therapy (for ≥3 months)</p>		<p>time to clinical worsening, and safety</p>	<p>The addition of sildenafil resulted in longer time to clinical worsening, with a smaller proportion of patients experiencing a worsening event in the sildenafil group than in the placebo group by week 16 ($P=0.002$).</p> <p>Of the side effects generally associated with sildenafil treatment, the most commonly reported in the placebo and sildenafil groups, respectively, were headache (34 and 57%), dyspepsia (2 and 16%), pain in extremity (18 and 25%), and nausea (18 and 25%). There were no P values reported.</p>
<p>Galie et al²⁷ (PHIRST)</p> <p>Tadalafil 2.5, 10, 20, or 40 mg daily</p> <p>vs placebo</p> <p>Patients taking a maximal stable dose of 125 mg bosentan twice daily for a minimum of 12 weeks at the time of screening continued on bosentan in addition to study medication.</p> <p>All patients who completed the 16-week, DB study (or who discontinued because of clinical worsening and who were not receiving tadalafil 40 mg) were</p>	<p>DB, DD, MC, PC, RCT (1:1:1:1)</p> <p>Patients (mean ages 53 to 55 years) with symptomatic PAH (idiopathic/heritable or related to anorexigen use, connective tissue disease, HIV infection, or congenital systemic-to-pulmonary shunts), either treatment-naïve or on background therapy with bosentan</p>	<p>N=405</p> <p>16 weeks (357 patients were enrolled in the extension study [334 out of 341 who completed the randomized 16-week study and 23 patients who prematurely discontinued the study because of clinical worsening]; as of October 2007, 213 of 357 patients (60%) enrolled in the extension study had</p>	<p>Primary: Change from baseline in 6MWD</p> <p>Secondary: Changes in WHO functional class and Borg dyspnea score, time to clinical worsening, changes in hemodynamic parameters, quality of life by the Medical Outcomes Study SF-36 and the EuroQol-5D questionnaire, and safety</p>	<p>Primary: Tadalafil increased the 6MWD in a dose-dependent manner. Only the 40-mg dose met the prespecified level of statistical significance ($P<0.01$) with a mean placebo-corrected treatment effect of 33 m. The treatment effect was 44 m ($P<0.01$) in bosentan-naïve patients compared to 23 m ($P=0.09$) in patients on background bosentan.</p> <p>The mean change from baseline in the 6MWD for patients enrolled in the extension study was 37 m after 16 weeks of treatment and 38 m after 44 weeks of treatment (P values not reported).</p> <p>Secondary: Changes in WHO functional class and Borg dyspnea score were not statistically different between the tadalafil and placebo groups (P values not reported). Tadalafil 40 mg significantly increased the time to clinical worsening ($P=0.041$) and reduced the incidence of clinical worsening (68% RR reduction; $P=0.038$). Improvements in mean pulmonary artery pressure ($P=0.01$), pulmonary vascular resistance ($P=0.039$), and cardiac index ($P=0.028$) were reported in patients receiving tadalafil 40 mg compared to baseline.</p> <p>Compared to placebo, statistically significant improvements were observed in six of the eight domains of the Medical Outcomes Study SF-36 health survey (all $P<0.01$) and for all sections of the EuroQol-5D questionnaire (all $P<0.02$) in the tadalafil 40 mg group.</p> <p>All doses of tadalafil were generally well tolerated, with the most common adverse events being headache, myalgia and flushing.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
eligible for a long-term extension study and received either tadalafil 20 (those who received this dose during the 16-week study) or 40 mg (all other doses groups) in a blinded fashion.		received tadalafil for at least 10 months)		
<p>McLaughlin et al²⁸ (TRIUMPH-1)</p> <p>Treprostinil 18 µg inhaled four times daily, titrated up over the first two weeks to 54 µg four times daily if tolerated</p> <p>vs</p> <p>placebo</p> <p>Patients were also receiving either bosentan or sildenafil therapy.</p>	<p>DB, MC, PC, RCT</p> <p>Patients 18 to 75 years of age with idiopathic or familiar PAH or PAH associated with collagen vascular disease, HIV infection, or anorexigen use (NYHA class III or IV symptoms), receiving bosentan or sildenafil for ≥3 months prior to study</p>	<p>N=235</p> <p>12 weeks</p>	<p>Primary: Change in 6MWD measured at peak (10 to 60 minutes after inhalation)</p> <p>Secondary: Time to clinical worsening, Borg Dyspnea Score, NYHA functional class, PAH signs and symptoms, trough 6MWD (at least four hours after drug administration), peak 6MWD at six weeks, and quality of life as measured by the MLWHF questionnaire</p>	<p>Primary: After 12 weeks, between-treatment median difference in change from baseline in peak 6MWD was 20 m ($P=0.0004$). Between-treatment median difference in change in peak 6MWD was 25 m ($P=0.0002$) in patients receiving background bosentan therapy and 9 m in patients taking sildenafil background therapy (P value not significant).</p> <p>Secondary: There was no difference in time to clinical worsening between treatment groups, no change in Borg Dyspnea Score, NYHA functional classification, and PAH signs and symptoms from baseline to week 12 compared to placebo.</p> <p>At week six, between-treatment median difference in change in peak 6MWD was 19 m ($P=0.0001$); at week 12, the change in trough 6MWD was 14 m ($P=0.0066$).</p> <p>Patients receiving inhaled treprostinil had significant improvements in their quality of life as assessed by the MLWHF questionnaire, with between-treatment median difference of -4 in the global score ($P=0.027$) and -2 in the physical score ($P=0.037$).</p>
<p>Simonneau²⁹</p> <p>Treprostinil subcutaneous infusion initiated at 1.25</p>	<p>DB, MC, PC, RCT</p> <p>Patients aged 8 to 75 years with</p>	<p>N=470</p> <p>12 weeks</p>	<p>Primary: Exercise capacity measured by 6MWD</p>	<p>Primary: At week 12, the 6MWD improved by a median of 10 m in the treprostinil group and did not change in the placebo group (0 m). The difference in median distance walked between the two groups was 16 m (95% CI, 4.4 to 27.6; $P=0.006$). The treatment effect was greater in severely ill patients (based on</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>ng/kg/min then titrated based on symptoms and adverse effects up to a maximum allowed study dose of 22.5 ng/kg/min plus conventional therapy (anticoagulants, oral vasodilators, diuretics and cardiac glycosides)</p> <p>vs</p> <p>placebo plus conventional therapy</p>	<p>primary PAH or PAH associated with connective tissue diseases or with congenital systemic-to-pulmonary shunts and NYHA functional class of II to IV, significant pulmonary hypertension</p>		<p>Secondary: Composite score of signs and symptoms of PAH, Dyspnea-Fatigue Rating, clinical deterioration, Borg Dyspnea score, cardiopulmonary hemodynamics, and global, physical and emotional quality of life measured by the MLWHF questionnaire</p>	<p>NYHA functional class) compared to less ill patients (51±16 m; $P=0.002$ vs -2±12 m; $P=0.869$). In addition, a dose effect was observed; the patients with doses in the highest quartile had the greatest improvement in 6MWD and patients in the first and second quartile had small improvements ($P=0.03$).</p> <p>Secondary: At 12 weeks, the signs and symptoms composite score in the treprostinil group improved from 7.6±0.5 at baseline to 8.5±0.5 and worsened in the placebo group from 7.5±0.4 at baseline to 7.4±0.2 ($P<0.0001$). The Dyspnea-Fatigue Rating in the treprostinil group improved from 4.2±0.1 at baseline to 5.4±0.2 and worsened in the placebo group from 4.4±0.1 at baseline to 4.3±0.1 ($P<0.0001$). The overall clinical deterioration, including deaths, transplantations, and discontinuation was 13 patients in the treprostinil group and 16 patients in the placebo group.</p> <p>At 12 weeks, the Borg Dyspnea score in the treprostinil group improved from 4.3±0.2 at baseline to 3.2±0.2 and improved in the placebo group from 4.4±0.2 at baseline to 4.2±0.2 ($P<0.0001$). There were significant improvements in the treprostinil group compared to the placebo group in mean right arterial pressure ($P=0.0002$), mean pulmonary artery pressure ($P=0.0003$), cardiac index ($P=0.0001$), pulmonary vascular resistance ($P=0.0001$), systemic vascular resistance ($P=0.0012$) and mixed venous oxygen saturation ($P=0.0001$). Patients in the treprostinil group has significant improvement in the in their physical dimension score ($P=0.0064$), but not the global dimension score ($P=0.17$) as compared with the placebo group.</p> <p>The adverse events that occurred more commonly in the treprostinil group were infusion site pain and reaction, diarrhea, jaw pain, flushing and edema.</p>

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RR=relative risk
 Miscellaneous abbreviations: EuroQol=European quality of life questionnaire, HIV=human immunodeficiency virus, MLWHF=Minnesota Living with Heart Failure, mm Hg= millimeters in mercury, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, SF-36=short form-36 health survey, WHO=World Health Organization, 6MWD=6-minute walk distance

Special Populations**Table 5. Special Populations¹⁻⁹**

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ambrisentan	No dosage adjustment required in elderly patients. Safety and efficacy in children have not been established.	No dosage adjustment in mild to moderate renal impairment required.	Not studied in hepatic dysfunction. Not recommended in patients with moderate or severe hepatic impairment.	X	Unknown; breastfeeding not recommended.
Bosentan	Not studied in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	Not studied in moderate or severe hepatic dysfunction. Not recommended in patients with moderate or severe hepatic impairment.	X	Unknown
Epoprostenol	Not studied in the elderly. Safety and efficacy in children have not been established.	Not reported	Not reported	B	Unknown
Iloprost	Not studied in the elderly. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown
Sildenafil	Not studied in the elderly. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild to moderate dysfunction. Not studied in severe dysfunction.	B	Unknown
Tadalafil	No dosage adjustment required in the elderly.	Dosage adjustment is required for patients with	Dosage adjustment is required for patients with	B	Unknown

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.	mild-to-moderate dysfunction. Use is not recommended in patients with severe dysfunction.	mild-to-moderate dysfunction. Use is not recommended in patients with severe dysfunction.		
Treprostinil inhalation solution	Not studied in the elderly. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Dosage adjustment is required for patients with mild-to-moderate dysfunction. Not studied in severe dysfunction.	B	Unknown
Treprostinil sodium injection	Not studied in the elderly. Safety and efficacy in children have not been established.	Not studied in renal dysfunction.	Dosage adjustment is required for patients with mild-to-moderate dysfunction. Not studied in severe dysfunction.	B	Unknown

Adverse Drug Events

The adverse events described in the package inserts are listed in Table 6. Adverse events vary by class of pulmonary arterial hypertension agent. Common adverse events in the class of prostanoids are jaw pain, diarrhea, headache and flushing. Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests. The phosphodiesterase -5 inhibitors are generally well tolerated and common adverse effects are headache, flushing and dyspepsia.

Table 6. Adverse Drug Events (%)¹⁻⁹

Adverse Event(s)	Ambrisentan	Bosentan	Epoprostenol	Iloprost	Sildenafil	Tadalafil	Treprostinil Inhalation Solution	Treprostinil Sodium Injection
Abdominal pain	-	-	5 to 27	-	-	-	-	-
Anemia	7 to 10	3 to 6	-	-	-	-	-	-
Anorexia	-	-	66	-	-	-	-	-
Anxiety/nervousness/agitation	-	-	11 to 21	-	-	-	-	-
Arthralgia	-	-	6 to 84	-	-	-	-	-
Arthritis	-	-	52	-	-	-	-	-
Arrhythmia	-	-	27	-	-	-	-	-
Back pain	-	-	-	-	-	10 to 12	-	-
Bradycardia	-	-	5 to 15	-	-	-	-	-
Bronchospasm	-	-	✓	-	-	-	-	-
Chest pain	-	-	11 to 67	-	-	-	-	-
Cough increased	-	-	-	39	-	-	54	-
Depression/depression psychotic	-	-	13	-	-	-	-	-
Diarrhea	-	-	37 to 50	-	-	-	-	25
Dizziness	-	-	8 to 83	-	-	-	-	-
Dyspepsia	-	-	-	-	13	10 to 13	-	-
Elevated alanine aminotransferase and aspartate aminotransferase	-	11 to 14	-	-	-	-	-	-
Eczema/rash/urticaria	-	-	25	-	-	-	-	-
Epistaxis	-	-	-	-	9	-	-	-
Erythema	-	-	-	-	6	-	-	-
Flu-like symptoms	-	-	13 to 25	-	-	-	-	-
Flushing	-	-	23 to 58	27	10	6 to 13	15	11
Headache	15	15	46 to 83	30	46	32 to 42	47	27
Hearing impairment	-	-	-	-	✓	✓	-	-
Hematuria	-	-	5	-	-	-	-	-
Hemorrhage	-	-	11 to 19	-	-	-	-	-
Hypesthesia/hyperesthesia/paresthesia	-	-	1 to 12	-	-	-	-	-
Hypotension	-	-	4 to 27	11	✓	✓	-	-
Insomnia	-	-	4 to 9	8	7	-	-	-
Infusion site pain	-	-	-	-	-	-	-	85
Infusion site reaction	-	-	-	-	-	-	-	83
Jaw pain	-	-	54 to 75	-	-	-	-	13

Adverse Event(s)	Ambrisentan	Bosentan	Epoprostenol	Iloprost	Sildenafil	Tadalafil	Treprostinil Inhalation Solution	Treprostinil Sodium Injection
Musculoskeletal pain	-	-	3 to 35	-	-	-	-	-
Myalgia	-	-	44	-	-	9 to 14	-	-
Nasal congestion	6	-	-	-	-	9	-	-
Nasopharyngitis	-	-	-	-	-	2 to 13	-	-
Nausea	-	-	-	13	-	10 to 11	19	22
Nausea/vomiting	-	-	32 to 67	-	-	-	-	-
Pain in extremity	-	-	-	-	-	5 to 11	-	-
Peripheral edema	17	11	-	-	-	-	-	9
Pleural effusion	-	-	7	-	-	-	-	-
Pneumonia	-	-	5	-	-	-	-	-
Respiratory tract infection	-	22	-	-	-	7 to 13	-	-
Skin ulcer	-	-	39	-	-	-	-	-
Sweating	-	-	1 to 41	-	-	-	-	-
Syncope	-	-	-	-	-	-	6	-
Tachycardia	-	-	1 to 35	-	-	-	-	-
Throat irritation/nasopharyngeal pain	-	-	-	-	-	-	25	-
Urinary tract infection	-	-	7	-	-	-	-	-
Vascular disorder	-	-	95	-	-	-	-	-
Vision Loss	-	-	-	-	✓	✓	-	-
Vomiting	-	-	7	-	-	-	-	-

✓ Percent not specified.

- Event not reported or incidence <1%.

Contraindications/Precautions^{1-9,30}

Ambrisentan and bosentan are contraindicated in women who are or may become pregnant. On March 4, 2011, the Food and Drug Administration removed a boxed warning about a potential for liver injury from the prescribing information for ambrisentan based on the review of post-marketing data; monthly liver function monitoring is no longer required. Bosentan, however, is still not recommended in patients with liver impairment. Due to serious contraindications, both drugs have black box warnings and can only be obtained through restricted distribution programs (see black box warnings below). In addition, endothelin receptor antagonists are associated with anemia, peripheral edema, and decreased sperm count. These agents should be discontinued in patients who develop pulmonary veno-occlusive disease.

Black Box Warning for Ambrisentan⁶

WARNING
<p>Contraindication: Pregnancy</p> <p>Ambrisentan is very likely to produce serious birth defects if used by pregnant women, as this effect has been seen consistently when it is administered to animals. Pregnancy must therefore be excluded before the initiation of treatment with ambrisentan and prevented during treatment and for one month after stopping treatment by the use of two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A IUD or LNG 20 IUS, in which case no additional contraception is needed. Obtain monthly pregnancy tests.</p> <p>Because of the risks of liver injury and birth defects, ambrisentan is available only through a special restricted distribution program called the LETAIRIS Education and Access Program (LEAP), by calling 1-866-664-LEAP (5327). Only prescribers and pharmacies registered with LEAP may prescribe and distribute ambrisentan. In addition, ambrisentan may be dispensed only to patients who are enrolled in and meet all conditions of LEAP.</p>

Black Box Warning for Bosentan⁷

WARNING
<p>Because of the risk of liver injury and birth defects, bosentan is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1 866 228 3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute bosentan. In addition, bosentan may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.</p> <p>Liver Injury</p> <p>In clinical studies, bosentan caused at least three-fold upper limit of normal (ULN) elevation of liver aminotransferases (aspartate aminotransferase and alanine aminotransferase) 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, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy with bosentan in patients with multiple co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of bosentan in these cases could not be excluded.</p> <p>In at least one case, the initial presentation (after >20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of bosentan. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping bosentan with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction.</p> <p>Elevations in aminotransferases require close attention. Bosentan should generally be avoided in patients with elevated aminotransferases (>3 times ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of</p>

WARNING

liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 times ULN, treatment with bosentan should be stopped. There is no experience with the re-introduction of bosentan in these circumstances.

Teratogenicity

Bosentan is likely to cause major birth defects if used by pregnant females based on animal data. Therefore, pregnancy must be excluded before the start of treatment with bosentan. Throughout treatment and for one month after stopping bosentan, females of childbearing potential must use two reliable methods of contraception unless the patient has a tubal sterilization or Copper T 380A IUD or LNG 20 IUS inserted, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective in patients receiving bosentan. Monthly pregnancy tests should be obtained.

Epoprostenol is contraindicated in patients with congestive heart failure due to severe left ventricular systolic dysfunction. Abrupt withdrawal of epoprostenol and treprostinil should be avoided as it may precipitate symptoms associated with rebound pulmonary hypertension. Epoprostenol, iloprost and treprostinil can inhibit platelet aggregation; therefore, there may be an increased risk of bleeding. Caution should be used in patient with hypotension as prostanoids may potentiate the effect. Epoprostenol should not be used chronically in patients who develop pulmonary edema during the administration, while iloprost and treprostinil should both be stopped immediately.

The phosphodiesterase (PDE)-5 inhibitors are contraindicated in patients using any form of organic nitrate regularly and/or intermittently. Sildenafil and tadalafil are not recommended in patients with pulmonary veno-occlusive disease or in patients with known hereditary degenerative retinal disorders, including retinitis pigmentosa. Sildenafil should be used cautiously in patients with the following: recent history of myocardial infarction, stroke, or life-threatening arrhythmia; hypotension (blood pressure $< 90/50$ mm Hg) or hypertension (blood pressure $> 170/110$ mm Hg); coronary artery disease causing unstable angina; and retinitis pigmentosa. Tadalafil should be prescribed with caution in patients with the following: cardiovascular disease, impaired autonomic control of blood pressure and aortic stenosis.

The PDE5 inhibitors should be used cautiously in patients with the following:

- Left ventricular outflow obstruction.
- Underlying cardiovascular disease that could be affected adversely by systemic vasodilatory properties such as decreases in blood pressure, and concurrent use of alpha-blockers and/or antihypertensive medications.
- Bleeding disorders or significant active peptic ulceration (active peptic ulcer disease).
- Anatomical deformation of the penis or conditions that may predispose them to priapism.

Drug Interactions

Table 7. Drug Interactions^{1-9,15}

Generic Name	Interacting Medication or Disease	Potential Result
Bosentan, sildenafil, tadalafil	Ritonavir	Ritonavir may increase bosentan concentration. Co-administration of ritonavir and sildenafil is not recommended. The dosage of tadalafil may require adjustment in patients receiving ritonavir.
Epoprostenol, iloprost, treprostinil	Antiplatelet agents and anticoagulants	Because epoprostenol, iloprost, and treprostinil inhibit platelet aggregation, there may be an increased risk of bleeding.
Epoprostenol,	Diuretics,	Concomitant administration may potentiate hypotensive effects.

Generic Name	Interacting Medication or Disease	Potential Result
iloprost, treprostinil	antihypertensives, vasodilators	
Ambrisentan, bosentan	Cyclosporine	Cyclosporine may increase ambrisentan exposure; limit the dose to 5 mg daily. Co-administration of bosentan and cyclosporine is contraindicated because it may lead to decreased cyclosporine and increased bosentan plasma concentrations.
Sildenafil, tadalafil	Alpha-blockers	Caution is advised when sildenafil and tadalafil are co-administered with alpha-blockers since both are vasodilators with blood pressure lowering effects.
Sildenafil, tadalafil	Azole antifungals	Concomitant use of sildenafil and potent CYP3A inhibitors is not recommended. The use of tadalafil should be avoided in patients taking itraconazole and ketoconazole.
Sildenafil, tadalafil	Nitrates (and nitric oxide donors)	Administration of sildenafil and tadalafil with nitrates in any form (regularly and/or intermittently) is contraindicated. Sildenafil and tadalafil may potentiate the hypotensive effects of nitrates. When nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. A suitable time interval following sildenafil dosing for the safe administration of nitrates or nitric oxide donors has not been determined.
Bosentan	Glyburide	Co-administration of bosentan and glyburide is contraindicated it may lead to increased risk of elevated liver enzymes.
Tadalafil	Rifampin	Rifampin may decrease tadalafil plasma concentration. Avoid use of tadalafil in patients receiving rifampin.

Dosage and Administration

Ambrisentan, bosentan and tadalafil may be taken without regard to food. The absorption of sildenafil may be decreased with a high fat meal.

Table 8. Dosing and Administration^{1-9,15,31}

Generic Name	Adult Dose	Pediatric Dose	Availability
Ambrisentan	<u>Treatment of PAH (WHO Group I) in patients with WHO class II or III symptoms to improve exercise ability and delay clinical worsening:</u> Tablet: initial, 5 mg QD; may increase up to 10 mg QD if 5 mg is tolerated; tablets should not be split, crushed or chewed	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Bosentan	<u>Treatment of PAH (WHO Group I) in patients with NYHA class II to IV symptoms to improve exercise ability and decrease clinical worsening:</u> Tablet: initial, 62.5 mg BID for 4 weeks; maintenance, 125 mg BID	Safety and efficacy in children have not been established.	Tablet: 62.5 mg 125 mg
Epoprostenol	<u>Long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma</u>	Safety and efficacy in children have not	Vial for injection: 0.5 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	<u>spectrum of disease in NYHA class III and class IV patients who do not respond adequately to conventional therapy:</u> Vial for injection via central venous catheter using ambulatory infusion pump: initial, 2 ng/kg/min; titrate up at increments of 2 ng/kg/min every 15 minutes or longer until dose-limiting effects or tolerance develops; if dose-limiting adverse effects occur, dose adjustments should be made gradually with decreases of 2 ng/kg/min every 15 minutes or longer; avoid abrupt withdrawal	been established.	1.5 mg This medication is available only through specialty pharmacies.
Iloprost	<u>Treatment of PAH (WHO Group I) in patients with NYHA class III or IV symptoms:</u> Ampule for inhalation: initial dose, 2.5 µg/dose; maintenance, 5 µg/dose if tolerated (otherwise, 2.5 µg/dose); administer six to nine times daily (no more frequently than every two hours) while awake; maximum, 45 µg daily	Safety and efficacy in children have not been established.	Ampule for inhalation: 10 µg/mL 20 µg/mL This medication is available only through specialty pharmacies.
Sildenafil	<u>Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening:*</u> Tablet: 20 mg TID, approximately 4 to 6 hours apart; doses above 20 mg TID are not recommended Vial for intravenous injection: 10 mg TID	Safety and efficacy in children have not been established.	Tablet: 20 mg Vial for injection: 0.8 mg/mL
Tadalafil	<u>Treatment of PAH (WHO Group I) to improve exercise ability:†</u> Tablet: 40 mg QD; dividing the dose over the course of the day is not recommended	Safety and efficacy in children have not been established.	Tablet: 20 mg
Treprostinil inhalation solution	<u>Treatment of PAH (WHO Group I) in patients with NYHA class III symptoms, to improve exercise ability:‡</u> Ampule for inhalation: initial, 18 µg (3 inhalations) QID while awake; if 3 inhalations are not tolerated, reduce to 1 or 2 inhalations, then increase to 3 inhalations as tolerated; maintenance, if tolerated, increase dose by an additional 3 inhalations at approximately 1 to 2 week intervals; maximum dose, 54 µg (9 inhalations) QID	Safety and efficacy in children have not been established.	Ampule for inhalation: 0.6 mg/mL This medication is available only through specialty pharmacies.
Treprostinil sodium injection	<u>Treatment of PAH (WHO Group I) to diminish symptoms associated with exercise and to reduce the rate of clinical deterioration in patients who require transition from epoprostenol:§</u> Vial for subcutaneous or intravenous continuous infusion: initial, 1.25 ng/kg/min; if dose is not tolerated, reduce to 0.625 ng/kg/min; increase infusion rate by 1.25 ng/kg/min weekly for the first four weeks, then	Safety and efficacy in children have not been established.	Vial for injection: 1 mg/mL 2.5 mg/mL 5 mg/mL 10 mg/mL This medication is available only through

Generic Name	Adult Dose	Pediatric Dose	Availability
	2.5 ng/kg/min weekly for the remainder of therapy; doses higher than 40 ng/kg/min have not been studied; avoid abrupt withdrawal		specialty pharmacies.

BID=twice daily, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, QD=once daily, QID=four times daily, TID=three times daily, WHO=World Health Organization

* Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).

† Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

‡ Studies included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

§ Studies included patients with NYHA class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology Foundation/ American Heart Association: Expert Consensus Document on Pulmonary Hypertension* (2009) ¹¹	<ul style="list-style-type: none"> Goals of treatment include improvement in the patient’s symptoms, quality of life, and survival. The optimal therapy for a patient should be individualized, taking into account many factors including: severity of illness, route of administration, side effects, comorbid illness, treatment goals, and clinician preference. Background therapies may include warfarin, diuretics, and/or oxygen depending on the patient’s diagnosis and symptoms. Oral calcium-channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing. The most commonly used CCBs include long acting nifedipine, diltiazem, and amlodipine, while verapamil should be avoided due to its potential negative inotropic effects. For patients who do not have a positive acute vasodilator response to testing and are considered lower risk based on clinical assessment, oral therapy with endothelin receptor antagonists (ERAs) or phosphodiesterase (PDE)-5 inhibitors would be the first line of therapy recommended. If an oral regimen is not appropriate, other treatments would need to be considered based on the patient’s profile and side effects and risk of each therapy. In general, patients with poor prognostic indexes should be initiated on intravenous epoprostenol or treprostinil therapy, while patients with class II or early III symptoms commonly commence therapy with either ERAs or PDE5 inhibitors. For patients who are considered high risk based on clinical assessment, continuous treatment with an intravenous prostacyclin (epoprostenol or treprostinil) would be the first line of therapy recommended. If a patient is not a candidate for continuous intravenous treatment, other therapies would have to be considered based on the patient’s profile, and side effects and risk of each treatment. Epoprostenol improves exercise capacity, hemodynamics, and survival in idiopathic pulmonary arterial hypertension (PAH) and is the preferred treatment option for the most critically ill patients. Although expensive and difficult to administer, epoprostenol is the only therapy for PAH that has been shown to prolong survival. Treprostinil may be delivered via either continuous intravenous or subcutaneous infusion. Iloprost is a prostacyclin analogue delivered by an adaptive aerosolized device six times daily. The ERAs are oral therapies that improve exercise capacity in PAH. Liver function tests must be monitored indefinitely on a monthly basis. PDE5 inhibitors also improve exercise capacity and hemodynamics in PAH. Combination therapy should be considered when patients are not

Clinical Guideline	Recommendations
	<p>responding adequately to initial monotherapy.</p> <p>(Note: at the time when this document was published, tadalafil and treprostinil inhalation solution were not Food and Drug Administration (FDA) approved for the treatment of PAH. In March 2011, the prescribing information for ambrisentan was updated to no longer require monthly monitoring of liver function tests.)</p>
<p>American College of Chest Physicians: Medical Therapy for Pulmonary Arterial Hypertension (2007)¹³</p>	<ul style="list-style-type: none"> • Warfarin and supplemental oxygen are recommended in selected patient populations. • In the absence of right-heart failure, patients with idiopathic PAH or PAH associated with underlying processes such as scleroderma or congenital heart disease, who demonstrate a favorable acute response to a vasodilator, should be considered candidates for a trial of therapy with an oral CCB. CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity. • PAH patients in functional class II who are not candidates for, or who have failed, CCB therapy, may benefit from treatment with sildenafil or subcutaneous or intravenous treprostinil. Although treprostinil is FDA approved for use in patients in functional class II, it would seldom be recommended due to the complexity of administration, side effects, and cost. • PAH patients in functional class III who are not candidates for, or who have failed, CCB therapy, are candidates for long-term therapy with ERAs or sildenafil, in no order of preference. Alternatives include intravenous epoprostenol, inhaled iloprost, or treprostinil. • PAH patients in functional class IV who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with intravenous epoprostenol (treatment of choice). Other treatments available, in no order of preference, include ERAs, inhaled iloprost, subcutaneous or intravenous treprostinil and sildenafil. <p>(Note: at the time when this document was published, ambrisentan, tadalafil and treprostinil inhalation solution were not FDA approved for the treatment of PAH.)</p>
<p>European Society of Cardiology/ European Respiratory Society: Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension† (2009)¹⁴</p>	<ul style="list-style-type: none"> • Selected patients with PAH may be candidates for supportive therapy with oral anticoagulants, diuretics, oxygen and digoxin. • Patients with idiopathic PAH and positive vasodilator response should be treated with a CCB. The CCBs commonly used in studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two. Nifedipine and amlodipine are recommended in patients with a relative bradycardia, while diltiazem is appropriate for patients with a relative tachycardia. • Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on a CCB because of potential severe side effects (e.g., hypotension, syncope, and right ventricular failure). • Non-responders to acute vasoreactivity testing who are in World Health Organization (WHO)-functional class II should be treated with an ERA or a PDE-5 inhibitor. • Non-responders to acute vasoreactivity testing, or responders who remain in (or progress to) WHO-functional class III should be considered candidates for treatment with either an ERA or a PDE5 inhibitor, or a prostanoid. • As head-to-head comparisons among different compounds are not

Clinical Guideline	Recommendations
	<p>available, no evidence-based first-line treatment can be proposed. The choice of the drug is dependent on a variety of factors including the approval status, the route of administration, the side effect profile, patients' preferences, and physicians' experience. Some experts still use first-line intravenous epoprostenol in WHO-functional class III patients because of its survival benefits.</p> <ul style="list-style-type: none"> • Continuous intravenous epoprostenol is recommended as first-line therapy for WHO-functional class IV PAH patients because of the survival benefit in this subset. Subcutaneous and intravenous treprostinil are also FDA-approved for the treatment of WHO-functional class IV patients. • Although ambrisentan, bosentan, and sildenafil are approved in WHO-functional class IV patients, only a small number of these patients were included in the randomized controlled trials of these agents. Therefore, most experts consider these treatments as a second line in severely ill patients. • In WHO-functional class IV patients, initial combination therapy should also be considered. In the case of inadequate clinical response, sequential combination therapy should be considered. • Combination therapy can include an ERA plus a PDE5 inhibitor, a prostanoid plus an ERA, or a prostanoid plus a PDE5 inhibitor. • Balloon atrial septostomy and/or lung transplantation are indicated for PAH with inadequate clinical response despite optimal medical therapy or where medical treatments are unavailable.

*This document was developed in collaboration with the American College of Chest Physicians, American Thoracic Society, and the Pulmonary Hypertension Association.

†This document was endorsed by the International Society of Heart and Lung Transplantation.

Conclusions

Pulmonary arterial hypertension (PAH) is a life-threatening disorder with a poor prognosis. There are three classes of drugs that are used to treat this disease, prostanoids, endothelin receptor antagonists (ERAs) and phosphodiesterase (PDE)-5 inhibitors.¹¹ Epoprostenol and treprostinil (Remodulin[®]) are available as continuous infusions.¹⁻³ Iloprost and treprostinil (Tyvaso[®]) are available as inhalation solutions.^{4,5} Ambrisentan, bosentan, sildenafil and tadalafil are available orally.⁶⁻⁹ Sildenafil is also available for intravenous administration.⁸ Only epoprostenol is currently available in a generic formulation.

Clinical trials have demonstrated the safety and efficacy of the PAH agents; however, there are no head-to-head trials comparing the agents within classes or between classes. The national and European consensus guidelines recommend oral therapy with either a PDE5 inhibitor or an ERA as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.^{11,13,14}

Parenteral therapy with prostanoids should be used first line in patients at higher risk and poor prognostic indexes. Epoprostenol is the preferred treatment for the most severely ill patients and is the only therapy shown to prolong survival.¹¹

Appendix I: Utilization Within This Drug Class for DVHA: October 1, 2010 to March 31, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
<i>Phosphodiesterase Inhibitors</i>					
Revatio	3	5	71.43%	\$13,703.73	\$2,740.75
Adcirca	1	2	28.57%	\$2,400.38	\$1,200.19
Class Total:	4	7	100%	\$16,104.11	\$2,300.59
<i>Endothelin Receptor Antagonists</i>					
Tracleer	2	3	100%	\$12,466.15	\$4,155.38
Class Total:	2	3	100%	\$12,466.15	\$4,155.38

Note: In the DVHA pharmacy benefit, there was no utilization for any agent in the prostanoid class.

Recommendations

In recognition of the following factors:

- National and European practice guidelines recommend oral therapy with either a phosphodiesterase (PDE)-5 inhibitor or endothelin receptor antagonist (ERA) as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.
- No head to head trials comparing the Pulmonary Arterial Hypertension (PAH) agents have been conducted.
- Only small studies have been conducted evaluating the efficacy of combination therapy.
- Ambrisentan and bosentan are available through a restricted distribution program and epoprostenol, iloprost, and treprostinil are distributed through specialty pharmacies.

... it is recommended that no changes be made to the current Department of Vermont Health Access (DVHA) approval criteria for phosphodiesterase (PDE)-5 inhibitors and endothelin receptor antagonists. However, in consideration of the cost of injectable prostanoids and the availability of a generic, it is recommended to move Flolan[®] to PA required with the following approval criteria:

Flolan[®]

- Clinical diagnosis of pulmonary hypertension
AND
- The patient has had a documented intolerance to the generic epoprostenol.

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