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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).¹⁻⁸ 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 available as a generic formulation.

PAH is characterized by elevated pulmonary arterial pressure and increased pulmonary vascular resistance leading to right heart failure.⁹ There is a poor prognosis associated with the disease and an approximate mortality rate of 15% within 1 year on therapy.⁹ The World Health Organization (WHO) classifies pulmonary hypertension into five groups.¹⁰ WHO Group 1 encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorder, portal hypertension, HIV infection, drugs and toxins, and other disorders that affect the small pulmonary muscular arterioles.¹¹ Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the level of disease using classes I to IV from little to significant impact on patient physical activity.¹¹

There are three classes of drugs that are FDA-approved for the treatment of WHO Group 1 PAH: prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase 5 (PDE5) inhibitors. In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I₂, a potent vasodilator and inhibitor of platelet aggregation.^{9,12} The prostanoids, epoprostenol, treprostinil, and iloprost, act as vasodilators and platelet aggregation inhibitors. 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.^{9,11} The actions of ET_A are vasoconstriction and cell proliferation and the actions of ET_B are vasodilatation and antiproliferation and endothelin-1 clearance.¹ The ERAs ambrisentan and bosentan competitively bind to the ET-1 receptors. Ambrisentan is highly selective for the ET_A receptor, while bosentan is an antagonist to both receptors with a slightly higher affinity for ET_A.^{1,2} However, the clinical significance of the affinities of the endothelin-1 receptor antagonists is unknown. PAH is also associated with impaired release of nitric oxide by the vascular endothelium resulting in reduction of cyclic guanosine monophosphate (cGMP) concentrations.⁶ PDE5 is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.⁵ Phosphodiesterase inhibitors increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.^{5,9}

The national consensus guidelines recommend oral therapy with either PDE5 inhibitors or ERAs as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.^{9,13} 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.⁹ At the time of the guidelines, inhaled treprostinil and tadalafil were not FDA-approved for the treatment of PAH.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Ambrisentan (Letairis [®])	Endothelin receptor antagonists	-
Bosentan (Tracleer [®])	Endothelin receptor antagonists	-
Epoprostenol (Flolan [®])	Prostanoids	✓
Iloprost (Ventavis [®])	Prostanoids	-
Sildenafil (Revatio [®])	Phosphodiesterase inhibitors	-
Tadalafil (Adcirca [®])	Phosphodiesterase inhibitors	-
Treprostinil inhalation solution (Tyvaso [®])	Prostanoids	-
Treprostinil sodium injection (Remodulin [®])	Prostanoids	-

Indications

Table 2. Food and Drug Administration Approved Indications¹⁻⁸

Indication	Ambrisentan	Bosentan	Epoprostenol	Iloprost	Sildenafil	Tadalafil	Treprostinil inhalation solution	Treprostinil sodium injection
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	✓	-	-	-	-	-	-	-
Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II to IV symptoms to improve exercise capacity 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 pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III or IV symptoms	-	-	-	✓	-	-	-	-
Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability and delay clinical worsening	-	-	-	-	✓	-	-	-
Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability	-	-	-	-	-	✓	-	-
Treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance	-	-	-	-	-	-	✓	-
Treatment of pulmonary arterial hypertension (PAH) in patients with NYHA Class II to IV symptoms, to diminish symptoms associated with exercise and to reduce the rate of clinical deterioration in patients who require transition from epoprostenol	-	-	-	-	-	-	-	✓

WHO=World Health Organization, NYHA=New York Heart Association

Pharmacokinetics**Table 3. Pharmacokinetics**^{1-8,9,14-17}

Generic Name	Bioavailability (%)	Tim to Peak plasma concentration	Excretion (%)	Metabolism (metabolites)	Serum Half-Life
Ambrisentan	80%; unaffected by food	2 hours	Primarily non-renal; relative contributions not well established	Hepatic: CYP3A, CYP2C19; UGT-1A9S, 2B7S, and 1A3S (4-hydroxy-methyl ambrisentan)	Terminal half-life 15 hours; effective half-life approximately 9 hours
Bosentan	50%; unaffected by food	3 to 5 hours	Biliary; renal: <3%	Hepatic: CYP3A, CYP2C9 (active: Ro 48-5033)	5 hours
Epoprostenol	Not reported	Not reported	82%urine 4%feces	Blood; extensively metabolized, rapid hydrolysis, enzymatic degradation (6-keto-PGF _{1α} , 6,15-diketo-13,14-dihydro-PGF _{1α})	≤ 6 minutes
Iloprost	Not reported	within minutes	68% urine 12% feces	Hepatic: β-oxidation (major), CYP450 (minor); (tetranor-iloprost)	20 to 30 minutes
Sildenafil	41%; high fat meal decreases absorption	30 to 120 minutes (mean: 60 minutes)	13% urine 80% feces	Hepatic:CYP3A 4 (major) and CYP2C9 (minor) (N-desmethyl metabolite)	4 hours
Tadalafil	Not reported; not affected by food	2 to 8 hours (median time of 4 hours)	36% urine 61% feces	Hepatic: CYP3A4	15 hours (healthy), 35 hours (pulmonary hypertension)
Treprostinil inhalation solution	64% (18 mcg), 72% (36 mcg)	0.25 and 0.12 hours	79% urine (4% unchanged); feces 13%	Hepatic: CYP2C8	4 hours
Treprostinil sodium injection	100%	Not reported	79% urine (4% unchanged, 64% metabolites); feces 13%	Hepatic: unknown enzymes (5 metabolites: HU1 through HU5)	4 hours

Clinical Trials

The safety and efficacy of ambrisentan for the treatment of PAH was established in the ARIES trials. ARIES-1 and ARIES-2 were randomized controlled trials of 12 weeks in a total of 394 patients that compared ambrisentan to placebo. The ambrisentan groups had a significant increase in exercise capacity as measured by the 6-minute walking distance (6MWD) compared to placebo.¹⁸ ARIES-E is the open-label extension study for ARIES-1 and ARIES-2. After 1 year of treatment, there was an improvement in 6MWD in the 2.5mg, 5mg, and 10mg ambrisentan groups (25 m, 28 m, and 37 m, respectively). After 2 years of treatment, the improvement was sustained in the 5mg and 10mg groups (23m and 28 m), but not the 2.5mg group (7 m).¹⁹

Bosentan was originally FDA-approved in patients with WHO functional class III and IV symptoms based on two double-blind, randomized, placebo controlled trials in 32 and 213 patients. These trials demonstrated a significant increase in the 6MWD in the bosentan groups compared to placebo.^{20,21} There was also a significant improvement in WHO functional class in the trials. Recently the FDA-approved indication was expanded to include patients with WHO functional class II symptoms based on the EARLY study. There was an increase in the 6MWD of 11.2 in the bosentan group and a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant.²² The study did show a significant delay in clinical worsening and lower incidence of worsening function class in the bosentan group compared to placebo.

Epoprostenol was evaluated in three randomized, open-label studies comparing epoprostenol plus conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or oxygen supplementation) and conventional therapy alone. One trial by Rubin et al demonstrated significant improvement in 6MWD and hemodynamic values compared to baseline, but the magnitude of differences between the groups was not statistically significant.¹² The other two trials by Barst et al and Badesch et al demonstrated significant differences in 6MWD and hemodynamic values compared to placebo.^{23,24}

The FDA-approval of iloprost was based on a randomized, placebo-controlled trial of 203 patients with PAH with NYHA class III or IV symptoms. The primary efficacy endpoint was clinical response defined as a composite of improvement in 6 MWD of 10%, improvement in at least one NYHA class, and no death or deterioration of pulmonary hypertension. After 12 weeks, there was a significant effect of treatment favoring iloprost.²⁵

The SUPER study evaluated sildenafil in a randomized, placebo-controlled trial of 278 patients. Sildenafil significantly improved exercise capacity, WHO functional class, and hemodynamics in patients with symptomatic PAH compared to placebo.²⁶ The addition of sildenafil to patients receiving epoprostenol was evaluated in PACES, a randomized, controlled trial of 267 patients. The sildenafil with epoprostenol group had improved exercise capacity, hemodynamic measurements, and time to clinical worsening in patients compared to the epoprostenol plus placebo group.²⁷

Safety and efficacy of tadalafil for the treatment of PAH was evaluated in the PHIRST study, a randomized, placebo controlled trial of 405 patients. Tadalafil significantly improved exercise capacity and reduced clinical worsening in patients compared to placebo.²⁸

The FDA-approval of treprostinil solution for inhalation was evaluated in the unpublished TRIUMPH-1 trial. After 12 weeks of treatment, there was a significant increase in the 6MWD in the treprostinil group compared to placebo.⁸

Treprostinil sodium for injection was evaluated in a randomized, placebo-controlled trial of 470 patients. After 12 weeks, there was a significant improvement in the 6MWD in the treprostinil group compared to placebo. There were also significant improvements in hemodynamic values in the treprostinil group.²⁹

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Galie et al¹⁸ (ARIES-1) Ambrisentan 5 mg or 10 mg daily vs placebo and (ARIES-2) Ambrisentan 2.5 mg or 5 mg daily vs placebo</p>	<p>DB, MC, PC, RCT (1:1:1) Patients (mean ages 49 to 53 years) with PAH, idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use)</p>	<p>ARIES-1 N=202 ARIES-2 N=192 12 weeks</p>	<p>Primary: Change from baseline in exercise capacity measured by 6MWD Secondary: Time to clinical worsening, change in WHO functional class, SF-36 Health Survey, 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 placebo-corrected 6MWD in ARIES-1 was 31 m (95% CI, 3 to 59; $P=0.008$) for ambrisentan 5mg and 51 m (95% CI, 27 to 76; $P<0.001$) for ambrisentan 10mg. In ARIES-2, the placebo-corrected 6MWD was 32 m (95% CI, 2 to 63; $P=0.022$) for ambrisentan 2.5mg and 59 m (95% CI, 30 to 89; $P=0.001$) for ambrisentan 5mg. Secondary: In ARIES-1 there was improvement in time to clinical worsening; however, it was not statistically significant compared to placebo in the 5 mg, 10 mg, and 5 mg 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 mg, 5 mg, and 2.5 mg and 5 mg combined groups compared to placebo ($P=0.005$, $P=0.008$, $P<0.001$, respectively). In ARIES-1, the distribution of WHO functional class significantly improved in the ambrisentan group compared placebo ($P=0.036$). In ARIES-2, the distribution WHO functional class in the ambrisentan group improved but it was not statistically significant versus placebo ($P=0.117$). In ARIES-1, there was 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 ambrisentan group compared to placebo ($P=0.005$). 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 (-0.9; 95% CI, -1.6 to -0.2; $P=0.002$) in ARIES-1 and for 2.5 mg (-1.0;</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>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 mg and 10 mg groups in ARIES-1 and the 2.5 mg 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. In the placebo group 3% discontinued due to adverse events and 2.3% discontinued due to adverse events in the ambrisentan group.</p>
<p>Oudiz et al¹⁹ (ARIES-E) Ambrisentan 2.5 mg, 5 mg, 10 mg</p>	<p>OL, ES, MC Patients (mean ages 49 to 52 years) with PAH that completed the ARIES-1 and ARIES-2 studies</p>	<p>N=350 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>Primary: After 1 year of treatment there was an improvement in 6MWD of 25 m (95% CI, 5 to 45 m) for 2.5 mg ambrisentan, 28 m (95% CI, 14 to 42 m) for 5 mg ambrisentan, and 37 m (95% CI, 22 to 52 m) for 10 mg ambrisentan groups. After 2 years of treatment, improvements were sustained in the 5 mg (23 m; 95% CI, 9 to 38 m) and the 10 mg (28; 95% CI, 11 to 45 m) groups, but not the 2.5 mg (7 m; CI, -13 to 27 m) group.</p> <p>After 1 year of treatment, there were improvements in Borg dyspnea scores for the 5 mg (-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 (-0.08; 95% CI, -0.55 to 0.38) group. The trend was similar after 2 years of treatments with changes in baseline of Borg dyspnea scores of -0.33 (95% CI, -0.68 to 0.03) for 5 mg, -0.60 (95% CI, -1.08 to -0.11) for 10 mg, and 0.23 (95% CI, -0.31 to 0.76) for 2.5 mg.</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 1 year and 88% (95% CI, 83% to 91%) at 2 years.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				<p>After 1 year, 83% (95% CI, 79% to 87%) of the overall population were free from clinical worsening and 72% (95% CI, 67% to 76%) were free from clinical worsening after 2 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>Channick et al²⁰</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 (6MWD)</p> <p>Secondary: Changes from baseline in cardiopulmonary hemodynamics Borg dyspnea index, WHO functional class, withdrawal due to clinical worsening</p>	<p>Primary: At week 12, the 6MWD significantly increased over 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>At week 12, the bosentan group had significantly improved cardiopulmonary hemodynamics compared to the placebo group. Pulmonary vascular resistance, pulmonary artery pressure, pulmonary capillary wedge pressure, and mean arterial pressure all significantly decreased compare 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 bosentan compared to placebo 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 $.01$; 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 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</p>

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				<p>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 3 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 abnormal hepatic function which was also the most frequent reason for discontinuation in the bosentan group.</p>
<p>Rubin et al²²</p> <p>(BREATHE-1)</p> <p>Bosentan 62.5 mg twice daily for 4 weeks then 125mg 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 scleroderma (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 6MWD</p> <p>Secondary: Change from baseline in Borg dyspnea index, WHO functional class, and time to clinical worsening</p>	<p>Primary: After 16 weeks, there was an increase in 6 MWD of 36 m in the bosentan group compared to a decrease of 8 m in the placebo group for a mean difference of 44 m (95% CI, 21 to 67; $P<0.001$).</p> <p>Secondary: After 16 weeks, the Borg dyspnea index had a mean decrease in of -0.1 ± 0.2 in the bosentan 125 mg group and -0.6 ± 0.2 in the bosentan 250 mg group and 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 bosentan 250 mg group (-0.9; $P=0.012$) compared to the bosentan 125 mg group (-0.4; $P=0.42$).</p> <p>At week 16, 38% of patients in the 125 mg group, 34% in the 25 mg group, and 28% in the placebo group had improved to WHO functional class II and 3% of patients in the 125 mg group, 1% in the 250 mg group and 0% in placebo group had improved to WHO functional class II. 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</p>

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<p>Galie et al²² (EARLY)</p> <p>Bosentan 62.5 mg twice daily for 4 weeks then 125 mg twice daily (or 62.5mg twice daily if <40 kg)</p> <p>vs</p> <p>placebo</p>	<p>DB, MC, PC, MC, PG, RCT</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 defect of less than 2 cm in diameter, ventricular septal defect of less than 1 cm in diameter, patent ductus arteriosus, or connective tissue or auto-immune diseases</p>	<p>N=185</p> <p>6 months</p>	<p>Primary: Change in baseline in pulmonary vascular resistance and 6MWD</p> <p>Secondary: Time to clinical worsening and change from baseline in WHO functional class, Borg dyspnea index, total pulmonary resistance, mean pulmonary arterial pressure, cardiac index, and mixed venous oxygen saturation</p>	<p>worsening compared to placebo ($P=0.004$).</p> <p>Primary: At 6 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 in the placebo group for a treatment effect of -22.6% (95% CI, -33.5 to -10.0; $P<0.0001$) favoring bosentan.</p> <p>At 6 months, the mean 6MWD increased in the bosentan group by 11.2 m (95% CI, -4.6 to 24.0) 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; $P=0.758$) favoring bosentan was not statistically significant.</p> <p>Secondary: There was a significant delay in time to clinical worsening with bosentan compared to placebo (HR, 0.227; 95% CI, 0.065 to 0.798; $P=0.0114$).</p> <p>At 6 months, there was a significantly lower incidence of worsening WHO functional class in the bosentan group with 3 patients (3.4%) vs 12 patients (13.2%) in the placebo group ($P=0.0285$). 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 arterial 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 placebo with a mean treatment effects 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</p>

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				most common adverse events in the bosentan group were nasopharyngitis and abnormal liver function tests.
Rubin et al ¹² Epoprostenol 1-2 ng/kg/min increased by 1-2 ng/kg/min every 5 to 15 minutes plus conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen) vs conventional therapy alone	OL, RCT, MC, PG Patients (age range 15 to 66 years) with primary PAH unresponsive or unable to tolerate oral vasodilators	N=24 8 weeks	Primary: Effect of epoprostenol on pulmonary hemodynamics and exercise tolerance	Primary: At 8 weeks there was a significant change from baseline in cardiac index ($P=0.020$), total pulmonary resistance ($P=0.022$), total systemic resistance ($P=0.0039$), and 6 MWD ($P=0.011$) 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. Adverse events seen in the study were not life-threatening and the most common included loose stools, jaw pain, and photosensitivity.
Barst et al ²³ Epoprostenol 4ng/kg below tolerated dose initially with dose adjustments made based on symptoms or adverse effects plus conventional therapy with anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen	OL, PRO, RCT, MC 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	N=81 12 weeks	Primary: Change in exercise capacity measured by 6MWD Secondary: Effects of epoprostenol on survival, quality of life, and hemodynamics	Primary: There was median change from baseline of 31 m increase in 6MWD in the epoprostenol group compared to a 29 m decrease in the conventional therapy group ($P<0.002$). Secondary: 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 the Chronic Heart Failure Questionnaire, two parts of the Nottingham Health Profile, and Dyspnea-Fatigue rating ($P<0.01$). The NYHA functional class improved in 16 patients (40%) vs 1 patient (3%), worsened in 5 (13%) vs 3 (10%), and was unchanged in 19 (48%) vs 27 (87%) in the epoprostenol and control groups, respectively

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs conventional therapy alone	oxygen			<p>($P < 0.002$).</p> <p>Epoprostenol had significant improvement of 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). There were significant differences in the changes between epoprostenol and control groups in the mean pulmonary artery pressure (-8% vs 3%; $P < 0.002$) and in the mean pulmonary vascular resistance (-21% vs 9%; $P < 0.001$).</p> <p>In the conventional therapy group, 8 patients died vs no patient 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>Minor complications were frequent and included jaw pain, diarrhea, flushing, headaches nausea, and vomiting. Serious complications were related to the drug delivery system.</p>
Badesch et al ²⁴ Epoprostenol ≤ 2 ng/kg initially then titrated based on symptoms and adverse effects plus conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen)	OL, RCT, MC Patients ≥ 16 years of age with PAH secondary to scleroderma spectrum disease	N=111 12 weeks	Primary: Exercise capacity measured by 6MWD Secondary: Effects of epoprostenol on cardiopulmonary hemodynamics, Borg dyspnea score, Dyspnea-	Primary: At week 12, there was an increase in the median 6MWD from 270 m to 316 m in the epoprostenol group and a decrease from 240 m to 192 m in the control group. The difference between the groups was 108 m (95% CI, 55.2 m to 180.0; $P = 0.001$). 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/m ² (95% CI, 0.39 to 0.81), 4.62%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs conventional therapy alone			Fatigue Rating, NYHA functional class, and severity of Raynaud phenomenon	<p>(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 control 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 compared to no patients in the control group that improved in NYHA functional class (<i>P</i> value not reported).</p> <p>There was a greater improvement in severity of Reynaud phenomenon over time in the epoprostenol group compared to control group with an AUC of 43.1±2.9 vs 52.3±3.2, respectively (<i>P</i>=0.038).</p> <p>The adverse events that occurred more commonly in the epoprostenol group included anorexia, nausea, diarrhea, and jaw pain.</p>
Olschewski et al ²⁵ Iloprost 5mcg 6 to 9 times daily vs placebo	MC, PC, MC, RCT Patients (mean ages 51 to 52 years) with primary PAH or appetite suppressant associated and scleroderma associated PAH despite use of conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen)	N=203 12 weeks	Primary: Clinical response as a composite of increase of at least 10% in 6MWD, and improvement in NYHA functional class in the absence of deterioration in clinical condition Secondary: Changes in 6MWD, NYHA class, Mahler	Primary: At 12 weeks there was a significant treatment effect in favor of iloprost (OR, 3.97; 95% CI, 1.47 to 10.75; <i>P</i> =0.007). In a secondary analysis of the primary endpoint, only treatment assignment contributed significantly to the probability of response (<i>P</i> =0.01). 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 (<i>P</i> =0.06). The mean change in 6MWD was significantly higher by 36.4 m in the iloprost group compared to the placebo group (<i>P</i> =0.004). At 12 weeks, significantly more patients in the iloprost group had improvement in NYHA functional class compared to the placebo group (<i>P</i> =0.03). There was no significant difference between the groups in number of patients with deterioration in NYHA functional class.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			<p>Dyspnea Index score, hemodynamic variables, and quality of life and clinical deterioration</p>	<p>After 12 weeks, cardiac output ($P<0.001$), systemic arterial oxygen saturation ($P<0.05$) and mixed venous oxygen saturation ($P<0.001$) decreased significantly and pulmonary vascular resistance ($P<0.05$) and right atrial pressure increased significantly 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, pulmonary artery pressure ($P<0.001$), pulmonary vascular resistance ($P<0.001$), systemic arterial pressure ($P<0.01$), and systemic arterial oxygen saturation ($P<0.05$) were significantly decreased and cardiac output ($P<0.001$) and pulmonary artery wedge pressure ($P<0.01$) were significantly increased.</p> <p>In the iloprost group, the Mahler Dyspnea Index score was significantly better compared to the placebo group at week 12 (change, 1.42 ± 2.59 vs 0.3 ± 2.45; $P<0.015$).</p> <p>In the iloprost group, the mean scores on the EuroQol visual-analogue scale improved significantly (46.9 ± 15.9 to 52.8 ± 19.1) and decreased in the placebo group (48.6 ± 16.9 to 47.4 ± 21.1; $P=0.026$). In the iloprost group, the mean scores on the EuroQol health-sate scale improved (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 1 patient died in the iloprost group compared to 4 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% in the placebo group ($P=0.41$). Overall, fewer patients died or deteriorated in the iloprost group compared to 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 al²⁶ (SUPER Study)</p> <p>Sildenafil 20 mg, 40 mg, or 80 mg by mouth three times daily</p> <p>vs</p> <p>placebo by mouth three times daily</p>	<p>DB, MC, PC, RCT (1:1:1:1)</p> <p>Patients (mean ages 47-51 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 6MWD</p> <p>Secondary: Change in mean pulmonary artery pressure, Borg dyspnea scale, and WHO functional class; incidence of clinical worsening; safety</p>	<p>Primary: The 6MWD increased from baseline in all sildenafil groups with the mean placebo-corrected treatment effects of 45 meters (13.0%), 46 meters (13.3%), and 50 meters (14.7%) for 20 mg, 40 mg, and 80 mg of sildenafil, respectively (all $P<0.001$). Among the 222 patients completing 1 year of treatment with sildenafil monotherapy, the improvement from baseline in the 6MWD was 51 meters.</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 mg, 40 mg, 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 the placebo group.</p> <p>The WHO functional class significantly improved in patients receiving all doses of sildenafil. After 12 weeks of treatment, the proportions of patients with an improvement of at least 1 functional class were 7% for placebo, and 28%, 36%, and 42% for sildenafil 20 mg, 40 mg, 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 al²⁷ (PACES)</p> <p>Sildenafil 20 mg three times daily titrated to</p>	<p>DB, MC, PC, PG, RCT</p> <p>Patients (mean age 48 years) with PAH (idiopathic,</p>	<p>N=267</p> <p>16 weeks</p>	<p>Primary: Change from baseline to week 16 in 6MWD</p> <p>Secondary:</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 meters for the sildenafil group and 1.0 meter for the placebo group ($P<0.001$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>40 mg and 80 mg three times daily, as tolerated, at 4-week intervals</p> <p>vs</p> <p>placebo</p> <p>Patients were also receiving IV epoprostenol therapy.</p>	<p>associated anorexigen use or connective tissue disease, or corrected congenital heart disease), who were receiving long-term IV epoprostenol therapy (for ≥ 3 months)</p>		<p>Change in hemodynamic parameters and Borg dyspnea scale, incidence of clinical worsening, safety</p>	<p>Secondary: Relative 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> <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%) (P values not reported).</p>
<p>Galie et al²⁸</p> <p>(PHIRST)</p> <p>Tadalafil 2.5 mg, 10 mg, 20 mg, or 40 mg by mouth daily</p> <p>vs</p> <p>placebo</p>	<p>DB, DD, MC, PC, RCT (1:1:1:1)</p> <p>Patients (mean ages 53-55 years) with symptomatic PAH (idiopathic/heritable or related to anorexigen use, connective tissue disease, human immunodeficiency virus infection, or congenital systemic-to-pulmonary shunts), either treatment-naïve or on background therapy with</p>	<p>N=405</p> <p>16 week</p>	<p>Primary: Change from baseline in 6MWD</p> <p>Secondary: Changes in WHO functional class and Borg dyspnea score, time to and incidence of clinical worsening, changes in hemodynamic parameters, 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 meters. The treatment effect was 44 meters ($P<0.01$) in patients who were bosentan-naïve compared with 23 meters ($P=0.09$) in patients on background bosentan.</p> <p>The mean change from baseline in the 6MWD for patients enrolled in the extension study was 37 meters after 16 weeks of treatment and 38 meters 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 lengthened 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 ($P=0.01$) and pulmonary vascular resistance</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	bosentan			($P=0.039$) were reported in patients receiving tadalafil 40 mg compared to baseline. All doses of tadalafil were generally well tolerated, with the most common adverse events being headache, myalgia, and flushing.
TRIUMPH-1 ⁸ (unpublished) Treprostinil 9 breaths (54mcg) inhaled 4 times daily vs placebo	DB, MC, PC, RCT Patients ≥ 18 years of age with PAH (WHO Group I and NYHA class III symptoms) receiving bosentan or sildenafil for ≥ 3 months prior to study	N=235 12 weeks	Primary: Change in 6MWD Secondary : Not reported	Primary: After 12 weeks, patients in the inhaled treprostinil group had a placebo-corrected median change in peak 6MWD from baseline of 20 m ($P<0.001$). When measured at trough exposure, patients in the inhaled treprostinil group had a placebo-corrected median change in 6MWD from baseline of 14 m (P value not reported).
Simonneau ²⁹ Treprostinil initiated at 1.25ng/kg/min then titrated based on symptoms and adverse effects up to a maximum allowed study dose of 22.5ng/kg/min plus conventional therapy (anticoagulants, oral vasodilators, diuretics, cardiac glycosides and/or supplemental oxygen) vs	DB, MC, PC, RCT Patients aged 8 to 75 years old with 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	N=470 12 weeks	Primary: Exercise capacity measured by 6MWD Secondary: Composite score of signs and symptoms of PAH, Dyspnea-Fatigue Rating, clinical deterioration, Borg Dyspnea score, cardiopulmonary hemodynamics, and global,	Primary: At week 12, there was a median improvement in the 6MWD of 10 m in the treprostinil group and no change in the placebo group (0 m). There was a median change between the groups of 16 m (95% CI, 4.4 m to 27.6 m; $P=0.006$). The treatment effect was greater in severely ill patients (based on NYHA functional class) compared to less sick 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 ($P=0.03$). 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 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 to 4.3 ± 0.1 ($P<0.0001$). The overall clinical deterioration, including deaths, transplantations, and discontinuation was 13 patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo plus conventional therapy			physical and emotional quality of life	<p>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 improve in the placebo group from 4.4±0.2 to 4.2±0.2 ($P<0.0001$). There was significant improvements in the treprostinil group compared to placebo 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 physical quality of life score compared to placebo ($P=0.0064$).</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

Miscellaneous abbreviations: EuroQol= European quality of life questionnaire, HIV=human immunodeficiency virus, NYHA= New York heart association, PAH=pulmonary arterial hypertension, PAP=pulmonary artery pressure, SF-36=short form-36 health survey

Special Populations

Table 5. Special Populations¹⁻⁸

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

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
	been established. No dosage adjustment required in the elderly.	patients with mild-to-moderate dysfunction. Use is not recommended in patients with severe dysfunction.	patients with mild-to-moderate dysfunction. Use is not recommended in patients with severe dysfunction.		
Treprostinil sodium injection	Safety and efficacy in children have not been established. Not studied in elderly.	Not studied in renal dysfunction.	Dosage adjustment is required for patients with mild-to-moderate dysfunction. Not studied in severe dysfunction.	Pregnancy Category B	Unknown
Treprostinil inhalation solution	Safety and efficacy in children have not been established. Not studied in elderly.	Not studied in renal dysfunction.	Dosage adjustment is required for patients with mild-to-moderate dysfunction. Not studied in severe dysfunction.	Pregnancy Category B	Unknown

Adverse Drug Events

The adverse events described in the package inserts are listed in Table 6. Adverse events vary by class of PAH agent. The most common adverse events in the prostanoids are jaw pain, diarrhea, headache and flushing. ERAs are associated with peripheral edema and elevated liver function tests. The PDE5 inhibitors are generally well tolerated and the most common adverse effects are headache, flushing, and dyspepsia.

Table 6. Adverse Drug Events¹⁻⁸

Adverse Event(s)	Ambrisentan	Bosentan	Epoprostenol	Iloprost	Sildenafil	Tadalafil	Treprostinil inhalation solution	Treprostinil sodium injection
Abdominal pain	-	-	5-27	-	-	-	-	-
Anemia	7-10	3-6	-	-	-	-	-	-
Anorexia	-	-	66	-	-	-	-	-
Anxiety/nervousness/ agitation	-	-	11-21	-	-	-	-	-
Arthralgia	-	-	6-84	-	-	-	-	-
Arrhythmia	-	-	27	-	-	-	-	-
Arthritis	-	-	52	-	-	-	-	-
Back pain	-	-	-	-	-	10-12	-	-
Bradycardia	-	-	5-15	-	-	-	-	-
Bronchospasm	-	-	✓	-	-	-	-	-
Chest pain	-	-	11-67	-	-	-	-	-
Cough increased	-	-	-	39	-	-	54	-
Depression/depression psychotic	-	-	13	-	-	-	-	-
Diarrhea	-	-	37-50	-	-	-	-	25
Dizziness	-	-	8-83	-	-	-	-	-
Dyspepsia	-	-	-	-	13	10-13	-	-
Elevated AST and ALT	0.8-2.8	11-14	-	-	-	-	-	-
Elevated AST and ALT								
Eczema/rash/urticaria	-	-	25	-	-	-	-	-
Epistaxis	-	-	-	-	9	-	-	-
Erythema	-	-	-	-	6	-	-	-
Flu-like symptoms	-	-	13-25	-	-	-	-	-
Flushing	-	-	23-58	27	10	6-13	15	11
Headache	-	-	46-83	30	46	32-42	47	27
Hearing impairment	-	-	-	-	✓	✓	-	-
Hematuria	-	-	5	-	-	-	-	-
Hemorrhage	-	-	11-19	-	-	-	-	-
Hypesthesia/ hyperesthesia/ paresthesia	-	-	1-12	-	-	-	-	-
Hypotension	-	-	4-27	11	✓	✓	-	-
Insomnia	-	-	4-9	8	7	-	-	-
Infusion site pain	-	-	-	-	-	-	-	85

Therapeutic Class Review: pulmonary arterial hypertension agents

Adverse Event(s)	Ambrisentan	Bosentan	Epoprostenol	Iloprost	Sildenafil	Tadalafil	Treprostinil inhalation solution	Treprostinil sodium injection
Infusion site reaction	-	-	-	-	-	-	-	83
Jaw pain	-	-	54-75	-	-	-	-	13
Musculoskeletal pain	-	-	3-35	-	-	-	-	-
Myalgia	-	-	44	-	-	9-14	-	-
Nasal congestion	-	-	-	-	-	9	-	-
Nasopharyngitis	-	-	-	-	-	2-13	-	-
Nausea	-	-	-	13	-	10-11	19	22
Nausea/vomiting	-	-	32-67	-	-	-	-	-
Pain in extremity	-	-	-	-	-	5-11	-	-
Peripheral edema	14	11	-	-	-	-	-	9
Pleural effusion	-	-	7	-	-	-	-	-
Pneumonia	-	-	5	-	-	-	-	-
Respiratory tract infection	-	22	-	-	-	7-13	-	-
Skin ulcer	-	-	39	-	-	-	-	-
Sweating	-	-	1-41	-	-	-	-	-
Syncope	-	-	-	-	-	-	6	-
Tachycardia	-	-	1-35	-	-	-	-	-
Throat irritation/ nasopharyngeal pain	-	-	-	-	-	-	25	-
Urinary tract infection	-	-	7	-	-	-	-	-
Vascular disorder	-	-	95	-	-	-	-	-
Vision Loss	-	-	-	-	✓	✓	-	-
Vomiting	-	-	7	-	-	-	-	-

AST=aspartate aminotransferase, ALT=alanine aminotransferase

Contraindications / Precautions¹⁻⁸

Ambrisentan and bosentan are contraindicated in women who are or may become pregnant. They are also not recommended in patients with liver impairment. Due to these serious contraindications, both drugs have black box warnings and can only be obtained through a restricted distribution program (see black box warning below). In addition, endothelin receptor antagonists are associated with anemia, peripheral edema, and decreased sperm counts.

Black Box Warning for Ambrisentan

WARNING

Warning: Potential liver injury

Ambrisentan can cause elevation of liver aminotransferases (ALT and AST) to at least 3 times the upper limit of normal (ULN). Ambrisentan treatment was associated with aminotransferase elevations >3 x ULN in 0.8% of patients in 12-week trials and 2.8% of patients including long-term open-label trials out to one year. One case of aminotransferase elevations >3 x ULN has been accompanied by bilirubin elevations >2 x ULN. Because these changes are a marker for potentially serious liver injury, serum aminotransferase levels (and bilirubin if aminotransferase levels are elevated) must be measured prior to initiation of treatment and then monthly.

In the post-marketing period with another endothelin receptor antagonist (ERA), bosentan, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy. In at least one case with bosentan, a late 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 the suspect drug. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment.

Elevations in aminotransferases require close attention. Ambrisentan should generally be avoided in patients with elevated aminotransferases (>3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin >2 x ULN, treatment should be stopped. There is no experience with the re-introduction of ambrisentan in these circumstances.

Contraindication: Pregnancy

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.

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.

Black Box Warning for Bosentan

WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

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

WARNING: RISKS OF LIVER INJURY and TERATOGENICITY

addition, bosentan may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.

Liver Injury

In clinical studies, bosentan caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, 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.

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.

Elevations in aminotransferases require close attention. Bosentan should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring liver injury may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin $\geq 2 \times$ 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. 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.

PDE5 inhibitors are contraindicated in patients using any form of organic nitrate either regularly and/or intermittently. Tadalafil should be prescribed with caution in the following patients: patients with unstable angina; heart failure; recent history of life-threatening arrhythmia, myocardial infarction, or stroke; hypotension (<90/50 mm Hg); uncontrolled hypertension (>170/100 mm Hg); pulmonary veno-occlusive disease; known hereditary degenerative retinal disorders, including retinitis pigmentosa. Sildenafil is not recommended in patients with pulmonary veno-occlusive disease and should be used cautiously in patients with the following: recent history of myocardial infarction, stroke, or life-threatening arrhythmia; hypotension (<90/50 mm Hg) or hypertension (BP >170/110 mm Hg); cardiac failure or coronary artery disease causing unstable angina; and retinitis pigmentosa.

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^{1-8,14}

Generic Name	Interacting Medication or Disease	Potential Result
Bosentan	Cyclosporine	Co-administration of bosentan and cyclosporine is contraindicated because it may lead to decreased cyclosporine and increased bosentan plasma concentrations.
Bosentan	Glyburide	Co-administration of bosentan and glyburide is contraindicated because it may lead to increased risk of elevated liver enzymes.
Bosentan, sildenafil, tadalafil	Ritonavir	Administration of ritonavir and bosentan may lead to increased bosentan concentrations. Co-administration of ritonavir and sildenafil is not recommended. The dosage of tadalafil may require adjustment in patients receiving ritonavir.
Epoprostenol, iloprost, treprostinil	Diuretics, antihypertensives, vasodilators	Concomitant administration may potentiate hypotensive effects.
Epoprostenol, iloprost, treprostinil	Antiplatelet agents and anticoagulants	Because epoprostenol, iloprost, and treprostinil inhibit platelet aggregation, there may be an increased risk of bleeding.
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 (either 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.
Tadalafil	Rifampin	Tadalafil should be avoided in patients receiving rifampin.

Dosage and Administration

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

Table 8. Dosing and Administration^{1-8,14}

Generic Name	Adult Dose	Pediatric Dose	Availability
Ambrisentan	Oral: initial, 5 mg once daily; may increase up to 10 mg daily if 5 mg tolerated. Tablets should not be split, crushed or chewed.	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg This medication is available only after enrollment in the medication-specific safety program.
Bosentan	Oral: initial, 62.5 mg twice daily for two weeks; maintenance, 125 mg twice daily.	Safety and efficacy in children have not been established.	Tablet: 62.5 mg 125 mg This medication is available only after enrollment in the medication-specific safety program.
Epoprostenol	Intravenous (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. Abrupt withdrawal should be avoided.	Safety and efficacy in children have not been established.	Vial for injection: 0.5 mg 1.5 mg This medication is available only through specialty pharmacies.
Iloprost	Inhalation: initial dose, 2.5 mcg inhaled; if tolerated, increase to maintenance 5.0 mcg; otherwise, keep maintenance at 2.5mcg. Dosing frequency is 6 to 9 times per day (no more than every 2 hours) during waking hours. Maximum dose: 45 mcg (5 mcg 9 times per day).	Safety and efficacy in children have not been established.	Ampule, for inhalation: 10 mcg/ml 20 mcg/ml This medication is available only through specialty pharmacies.
Sildenafil	Oral: 20 mg three times daily, approximately 4-6 hours apart; doses above 20 mg three times daily are not recommended.	Safety and efficacy in children have not been established.	Tablet: 20 mg
Tadalafil	Oral: 40mg once daily; dividing the dose over the course of the day is not recommended.	Safety and efficacy in children have not been established.	Tablet: 20 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
Treprostinil inhalation solution	Inhalation: initial, 18 mcg (3 breaths) per treatment session four times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated; maintenance: dosage should be increased by an additional 3 breaths at approximately 1-2 week intervals, if tolerated, until the target and maximum dose of 54 mcg of treprostinil (9 breaths) is reached per treatment session four times daily.	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	Subcutaneous or intravenous (continuous infusion): initial, 1.25 ng/kg/min; if initial dose is not tolerated, infusion rate should be decreased to 0.625 ng/kg/min. Increase in infusion rate should be 1.25 ng/kg/min every week for the first 4 weeks then 2.5 ng/kg/min for the remaining duration of infusion depending on clinical response. Doses higher than 40 ng/kg/min have not been studied. Abrupt withdrawal should be avoided.	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 specialty pharmacies.

Drug Acquisition Cost

Table 9. Drug Acquisition Cost

Medication	Dosage Form	Strengths	Cost Per Unit*
Adcirca [®]	Tablet	20 mg	\$19.61
Epoprostenol	Vial	0.5 mg 1.5 mg	\$14.46 \$34.93
Flolan [®]	Vial	0.5 mg 1.5 mg	\$21.36 \$51.59
Letairis [®]	Tablet	5 mg 10 mg	\$217.20
Remodulin [®]	Vial	1 mg/ml 2.5 mg/ml 5 mg/ml 10 mg/ml	\$1,345.00 \$3,362.50 \$6,725.00 \$13,450.00
Revatio [®]	Tablet	20 mg	\$17.16
Tracleer [®]	Tablet	62.5 mg 125 mg	\$108.60
Tyvaso [®]	Inhalation solution	0.6 mg/ml	\$15,049.61 (starter kit) \$13,419.92 (refill kit)
Ventavis [®]	Inhalation solution	10 mcg/ml 20 mcg/ml	\$74.40

*AWP per RxClaim as of 1/19/10

Potential Advantages/Potential Disadvantages/Unanswered Questions

- No head to head trials comparing the PAH agents.
- Only small studies evaluating the effect of combination therapy.
- Ambrisentan and bosentan are distributed through a restricted distribution program and epoprostenol, iloprost, and treprostinil are distributed through specialty pharmacies.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
<p>American College of Cardiology Foundation (ACCF)/American Heart Association (AHA): Expert Consensus Document on Pulmonary Hypertension* (2009)⁹</p>	<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 patients’ diagnosis and symptoms. Oral calcium-channel blockers (CCB) are indicated only for patients who have a positive acute vasodilator response to testing. • For patients who did not have a positive acute vasodilator response to testing and are considered lower risk based on clinical assessment, oral therapy with endothelin receptor antagonists or PDE5 inhibitors would be the first line of therapy recommended. If an oral regimen is not appropriate, the other treatments would need to be considered based on 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 endothelin receptor antagonists or PDE5 inhibitors. • For patients who are considered high risk based on clinical assessment, continuous treatment with intravenous (IV) prostacyclin (epoprostenol or treprostinil) would be the first line of therapy recommended. If a patient is not a candidate for continuous IV 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 IV or subcutaneous (SC) infusion. Iloprost is a prostacyclin analogue delivered by an adaptive aerosolized device 6 times daily. The endothelin receptor antagonists 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 responding adequately to initial monotherapy. <p>(Note: at the time when this document was published, tadalafil and treprostinil inhalation solution were not FDA approved for the treatment of PAH.)</p>
<p>American College of Chest Physicians (ACCP):</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

Clinical Guideline	Recommendations
<p>Medical Therapy for Pulmonary Arterial Hypertension (2007)¹³</p>	<p>associated with underlying processes such as scleroderma or congenital heart disease, who demonstrate a favorable acute response to 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.</p> <ul style="list-style-type: none"> • PAH patients in functional class II who are not candidates for, or who have failed, CCB therapy, may benefit from treatment with sildenafil or SC or IV 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 endothelin-receptor antagonists or sildenafil, in no order of preference; IV epoprostenol; inhaled iloprost; or SC or IV 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 IV epoprostenol (treatment of choice). Other treatments available, in no hierarchical order, include endothelin-receptor antagonists, inhaled iloprost, SC treprostinil, sildenafil, and IV treprostinil. <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>

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

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, ERAs and PDE5 inhibitors. Epoprostenol and treprostinil (Remodulin[®]) are available as continuous infusions. Iloprost and treprostinil (Tyvaso[®]) are available as inhalation solutions. Ambrisentan, bosentan, sildenafil, and tadalafil are available orally. Only epoprostenol is 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 consensus guidelines recommend oral therapy with either PDE5 inhibitors or endothelin receptor antagonists as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.^{9,13} Parenteral therapy 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.⁹

Appendix I: Other Insurance Coverage

Managed Care Organization	Current Coverage
MassHealth (Massachusetts Medicaid)	PA required: Adcirca [®] , Flolan [®] , Revatio [®] No PA required: epoprostenol, Letairis [®] , Remodulin [®] , Tracleer [®]
New Hampshire Medicaid	Preferred: Tracleer [®] Non-preferred: Letairis [®] , Revatio [®]
New York Medicaid	No Information
MVP Healthcare	PA required, Tier 3: Letairis [®] , Revatio [®] , Tyvaso [®] , Ventavis [®] PA required, medical benefit: Remodulin [®]

Managed Care Organization	Current Coverage
Cigna Healthcare	Tier 2: Revatio® Tier 3: Letairis®, Tracleer®, Tyvaso®, Ventavis® PA required, Tier 3: Adcirca®
Blue Cross Blue Shield of Vermont	PA required: Flolan®, Letairis®, Revatio®, Tracleer®, Ventavis®

Appendix II: Current Preferred Drug List (PDL) Alternatives

Medication	Cost/unit*	Dosing Frequency ^{1-9,14}	Cost/30 days
Adcirca® (tadalafil) 20mg tablet	\$19.61	40 mg once daily	\$1,176.60
Epoprostenol (Flolan®) 0.5 mg, 1.5 mg vial	\$14.46- \$34.93	Initial, 2 ng/kg/min; titrate up at increments of 2 ng/kg/min every 15 minutes or longer until does-limiting effects or tolerance develops. Dosing range: 25 ng/kg/min to 40 ng/kg/min	\$2,095.80- \$3,143.70
Flolan® (epoprostenol) 0.5 mg, 1.5 mg vial	\$21.36- \$51.59	Initial, 2 ng/kg/min; titrate up at increments of 2 ng/kg/min every 15 minutes or longer until does-limiting effects or tolerance develops. Dosing range: 25 ng/kg/min to 40 ng/kg/min	\$3,095.40- \$4,643.10
Letairis® (ambrisentan) 5 mg, 10 mg	\$217.20	5mg to 10 mg once daily	\$6,516.00
Remodulin® (treprostinil sodium injection) 1 mg/ml, 2.5 mg/ml, 5 mg/ml, 10 mg/ml vial	\$1,345.00- \$13,450.00	Initial, 1.25 ng/kg/min; increase in infusion rate: 1.25 ng/kg/min every week for the first 4 weeks then 2.5 ng/kg/min for the remaining duration. Maximum dose: 40 ng/kg/min	\$13,450.00
Revatio® (sildenafil) 20 mg tablet	\$17.16	20 mg three times daily	\$1,544.40
Tracleer® (bosentan) 62.5 mg, 125 mg tablet	\$108.60	125 mg twice daily	\$6,516.00
Tyvaso® (treprostinil inhalation solution) 0.6 mg/ml inhalation solution	\$15,049.61 (starter kit) \$13,419.92 (refill kit)	Initial 18 mcg (3 breaths) per treatment session four times daily. Maintenance: 54 mcg (9 breaths) four times daily.	\$15,049.61 (initial month) \$13,419.92 (subsequent months)
Ventavis® (iloprost) 10 mcg/ml, 20 mcg/ml	\$74.40	2.5 mcg to 5 mcg inhaled 6 to 9 times per day (no more than every 2 hours) during waking hours. Maximum dose: 45 mcg (5 mcg 9 times per day).	\$13,392.00- \$20,088.00

*AWP per RxClaim as of 1/19/10

Appendix III: Most Recent Utilization Within this Drug Class for OVHA: April 1, 2009 to September 30, 2009

Medication	# of Rx's	% Marketshare	Plan Cost \$	Avg \$/Rx
Remodulin [®]	8	50%	\$80,024.85	\$10,003.11
Revatio [®]	7	44%	\$15,254.90	\$2,179.27
Tracleer [®]	1	6%	\$5,147.50	\$5,147.50
Class Total:	16	100%	\$100,427.25	\$6,276.70

Recommendations

Ambrisentan and bosentan are only available through a restricted distribution program. Due to their routes of administration, epoprostenol, iloprost and treprostinil are supplied through specialty pharmacies. Currently, OVHA only requires prior authorization for sildenafil with approval criteria of clinical diagnosis of pulmonary hypertension and no concomitant use of organic nitrate-containing products. Ambrisentan, bosentan, epoprostenol, iloprost, and treprostinil sodium for injection are available without prior authorization. Therefore, the following are recommended:

- No changes to current status of epoprostenol, Flolan[®], Letairis[®], Remodulin[®], Revatio[®], Tracleer[®], and Ventavis[®].
- Tyvaso[®] made available without prior authorization.
- Adcirca[®] added to the PDL as prior authorization required with the same criteria as sildenafil:
 - Clinical diagnosis of pulmonary hypertension
 - No concomitant use of organic nitrate-containing products

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