

# Pulmonary Arterial Hypertension (PAH)

## Agents

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## Pulmonary Arterial Hypertension (PAH) Agents Review

### FDA-Approved Indications

Drug	Manufacturer	Indication(s)
<b>Oral Agents</b>		
ambrisentan (Letairis™) <sup>1</sup>	Gilead Sciences	<ul style="list-style-type: none"> <li>Treatment of pulmonary arterial hypertension (World Health Organization [WHO] Group I) in patients with WHO Class II or III symptoms, to improve exercise capacity and delay clinical worsening.</li> </ul>
bosentan (Tracleer®) <sup>2</sup>	Actelion	<ul style="list-style-type: none"> <li>Treatment of pulmonary arterial hypertension (WHO Group I) in patients with WHO Class II to IV symptoms, to improve exercise capacity and decrease the rate of clinical worsening.</li> </ul>
sildenafil (Revatio™) <sup>3</sup>	Pfizer	<ul style="list-style-type: none"> <li>Treatment of pulmonary arterial hypertension (WHO Group I), to improve exercise ability and delay clinical worsening.</li> </ul>
tadalafil (Adcirca™) <sup>4</sup>	Eli Lilly	<ul style="list-style-type: none"> <li>Treatment of pulmonary arterial hypertension (WHO Group I), to improve exercise ability.</li> </ul>
<b>Inhalation Agents</b>		
iloprost (Ventavis®) <sup>5</sup>	Actelion	<ul style="list-style-type: none"> <li>Treatment of pulmonary arterial hypertension (WHO Group I) in patients with New York Heart Association (NYHA) Class III or IV symptoms. In controlled trials, it improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.</li> </ul>
treprostinil (Tyvaso™) <sup>6</sup>	United Therapeutics	<ul style="list-style-type: none"> <li>Treatment of pulmonary arterial hypertension (WHO Group I) in patients with NYHA Class III symptoms, to increase walk distance.</li> </ul>

Benefits of bosentan (Tracleer) versus risk of liver injury in WHO Class II should be considered; early liver injury may preclude future use as disease progresses. Efficacy of sildenafil (Revatio) has not been adequately evaluated in patients currently on bosentan (Tracleer). Sildenafil (Viagra®) and tadalafil (Cialis®) are also FDA-approved for erectile dysfunction (ED).

### Overview

Pulmonary hypertension (PH) is characterized by an increase in pulmonary arterial pressure and secondary right ventricular failure. This is defined as a resting mean pulmonary arterial pressure (mPAP) >25 mm Hg or an mPAP with exercise >30 mm Hg. Pulmonary arterial hypertension (PAH) has the added criterion of pulmonary arterial wedge pressure of ≤15 mm

Hg.<sup>7</sup> Symptoms include dyspnea, dizziness, syncope, fatigue, edema (periphera), angina, palpitations, and other symptoms, all of which are exacerbated by exertion. The prevalence varies substantially depending on the type, etiology, and underlying condition; the prevalence is 15 per million.<sup>8</sup> PH does not have a cure and, if left untreated, PH is a life-threatening disease with poor prognosis. Although the number of approved therapies for PAH has grown in the past years, the prognosis is still poor, with approximately 50 percent mortality within the first five years after diagnosis.<sup>9</sup> Management of PH should be limited to specialized centers where clinicians are experienced in the evaluation and treatment of patients with PH.

There are many causes of PAH including idiopathic or sporadic disease and hereditary causes. There are cellular changes in the walls of pulmonary arteries, and it appears that mutations in the bone morphogenetic protein receptor type 2 (BMPR2) gene plays a key role in the pathogenesis of PAH.<sup>10</sup> Other etiologies in PAH include drugs and toxins, collagen vascular resistance, HIV, portal hypertension, and congenital heart disease.

Previously PH was either idiopathic pulmonary arterial hypertension (IPAH), formerly known as primary pulmonary hypertension (PPH), or secondary PH. In an effort to organize PH, the World Health Organization (WHO) has updated the PH nomenclature.<sup>11</sup> The WHO classifies PH patients into five groups based on etiology. Group I now refers to pulmonary arterial hypertension (PAH); the other four groups describe PH.<sup>12</sup> Each group has subgroups. Collectively all five groups are referred to as PH.

Measuring baseline severity in PH is important prior to initiation of therapy since response to therapy is measured as a change from baseline. Since functional and hemodynamic impairment are central in PH, patient's ability to function is measured by determining exercise capacity, which in turn determines the WHO functional class (FC).<sup>13</sup> The WHO FC classifications are: class I: no limitation of physical activity; class II: mild limitation of physical activity; class III: marked limitation of physical activity; class IV: inability to perform any physical activity.

The evidence-based American College of Chest Physicians (ACCP) PAH guidelines were initially released in 2007.<sup>14</sup> In 2009, two groups updated new PH guidelines.<sup>15,16</sup> The first was a joint PH Expert Consensus Document (ECD) from the American College of Cardiology Foundation (ACCF) Task Force on ECDs and the American Heart Association (AHA).<sup>17</sup> The ECD strives to inform practitioners and other interested parties of their opinions in this evolving area of clinical practice where rigorous evidence may not be available or the evidence to date is not widely accepted. The second was the result of the 4<sup>th</sup> World Symposium on Pulmonary Hypertension, which took place in Dana Point, CA, in 2008.<sup>18</sup> A resulting updated PAH evidence-based treatment algorithm was published in 2009 in the Journal of American College of Cardiology. The ECD is generally in line with the 4<sup>th</sup> World Symposium recommendations. It should be noted that different treatments have been evaluated mainly in idiopathic PAH, heritable PAH, and in PAH associated with the scleroderma spectrum of diseases or with anorexigen use. Therefore, caution is warranted when extrapolating these recommendations to other PAH subgroups.

The following is a summary of the evidence-based PAH treatment algorithm developed at the 4<sup>th</sup> World Symposium on PH.<sup>19</sup>

- Oral anticoagulation, diuretics, oxygen, and digoxin are recommended (expert opinion), but data on long-term effects are lacking.
- A trial of high dose oral calcium channel blockers (CCB) (Grade B) such as dihydropyridine type or diltiazem is recommended only in a minority of patients with

IPAH with a positive acute vasoreactive test. These patients should be followed closely for both safety and efficacy of this therapy. Patients with PAH due to conditions other than IPAH have a very low rate of long-term responsiveness to oral CCBs.

- Patients with a negative response to the acute vasoreactivity test or positive responders who are unable to maintain a sustained response to remain in WHO functional class I-II are considered candidates for treatment with prostacyclins, endothelin receptor antagonists (ERAs), or a phosphodiesterase-5 inhibitor (PDE-5 inhibitors).
  - ❖ WHO FC II: ambrisentan (Letairis), bosentan (Tracleer), and sildenafil (Revatio) (Grade A for all); Tadalafil (Adcirca) (Grade B)
  - ❖ WHO FC III: ambrisentan, bosentan, IV epoprostenol, inhaled iloprost (Ventavis), sildenafil (Grade A for all); Tadalafil, SC treprostinil (Remodulin<sup>®</sup>) (Grade B)
  - ❖ WHO FC IV: Continuous intravenous epoprostenol (Flolan<sup>®</sup>) (Grade A) – improves exercise capacity, hemodynamics, and survival in FC IV. This is the treatment of choice for the most critically ill patients. Epoprostenol is also the only therapy for PAH that has been shown to prolong survival. Inhaled iloprost (Grade B); SC treprostinil (Grade C)
- Combination therapy with two agents with different mechanisms of action is recommended in patients who are not responding adequately to PAH monotherapy. The optimal combination on the basis of overall risk-benefit remains unknown.
- Atrial septostomy and lung transplantation are indicated for refractory patients or where medical treatment is unavailable.

Tadalafil (Adcirca) and inhaled treprostinil (Tyvaso) were investigational at the time of the 4<sup>th</sup> World Symposium on PH.

The Food and Drug Administration (FDA) approved treatments for PAH include prostacyclin and prostacyclin analogs [IV epoprostenol (Flolan<sup>®</sup>), treprostinil (IV, SC Remodulin<sup>®</sup> / inhalation Tyvaso<sup>™</sup>), iloprost (Ventavis<sup>®</sup>)], oral endothelin receptor antagonists [bosentan (Tracleer) and ambrisentan (Letairis)] and oral phosphodiesterase 5 (PDE-5) inhibitors [sildenafil (Revatio) and tadalafil (Adcirca)]. This review will focus on oral medications [ambrisentan (Letairis), bosentan (Tracleer) sildenafil (Revatio), and tadalafil (Adcirca)] and inhaled medications [iloprost (Ventavis) and treprostinil (Tyvaso)] for the treatment of pulmonary arterial hypertension (PAH).

### **Pharmacology**<sup>20,21,22,23,24,25</sup>

Endothelin-1 (ET-1) is a neurohormone whose effects are mediated by binding to receptors in the endothelium and vascular smooth muscle. Increased ET-1 concentrations in the plasma and lung tissue occur in patients with PAH. Two receptor subtypes, ET<sub>A</sub> and ET<sub>B</sub>, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. Bosentan (Tracleer), a competitive antagonist at the endothelin receptor (ET<sub>A</sub> and ET<sub>B</sub>), was the first in this new drug class known as endothelin (ET-1) receptor antagonists. The newest agent in this class, ambrisentan (Letairis), is selective at the ET<sub>A</sub> receptor. Ambrisentan is a high affinity (K<sub>i</sub>=0.011 nM) ET<sub>A</sub> receptor antagonist with a high selectivity for the ET<sub>A</sub> versus ET<sub>B</sub> receptor (>4000-fold). The clinical impact of high selectivity for ET<sub>A</sub> or for dual endothelin blockage is unknown.

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

Iloprost (Ventavis) and treprostinil (Tyvaso) are inhaled prostacyclin analogues. Their major pharmacologic actions are direct vasodilation of pulmonary and systemic arterial vascular beds. They also inhibit platelet aggregation.

### Pharmacokinetics

Drug	Half-life	Bioavailability (%)	Metabolite	Excretion (%)
<b>Oral Agents</b>				
ambrisentan (Letairis) <sup>26</sup>	9 hr	Unknown	Unknown	Renal: minor Non-Renal: major
bosentan (Tracleer) <sup>27</sup>	5 hr	50	Two inactive and one active that contributes 10 ~ 20 percent of parent drug activity	Renal: 3 Feces: 97
sildenafil (Revatio) <sup>28</sup>	4 hr (for parent drug and metabolite)	41	N-desmethyl metabolite (active with <i>in vitro</i> potency of PDE-5 ~ 50 percent of parent drug)	Renal: 13 Feces: 80
tadalafil (Adcirca) <sup>29</sup>	*15 hr	Unknown	Major metabolite is methylcatechol glucuronide which is considered inactive	Feces: 61 Renal: 36
<b>Inhalation Agents</b>				
iloprost (Ventavis) <sup>30</sup>	20 to 30 minutes	Unknown	Main metabolite is tetranor-iloprost (inactive in animal studies)	Feces: 12 Renal: 68
treprostinil (Tyvaso) <sup>31</sup>	4 hours	64 to 72 (dose dependent)	Five inactive metabolites (four are products of oxidation of the 3-hydroxyoctyl side chain and one is a glucuroconjugated derivative: treprostinil glucuronide).	Feces: 13 Renal: 79

\*The half-life of tadalafil is 35 hours in PAH patients not receiving bosentan.

### **Contraindications/Warnings**<sup>32,33,34,35,36,37</sup>

Ambrisentan (Letairis) has two black box warnings related to potentially serious liver injury and the likelihood of serious birth defects if used by pregnant women. Elevation of liver transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] to at least three times the upper limit of normal (ULN) have occurred with the use of ambrisentan in 0.8 percent of patients in 12-week trials and 2.8 percent of patients including long-term, open-label trials up to one year. Elevations in aminotransferases require close attention. Additionally, ambrisentan is very likely to produce serious birth defects if used by pregnant women. Due to the risks of liver damage and birth defects, ambrisentan is available only through a special restricted distribution program for pharmacies, prescribers, and patients known as LEAP (Letairis Education and Access Program) by calling 1-866-664-5327.

Bosentan (Tracleer) also has two black box warnings related to potentially serious liver injury and teratogenicity. Bosentan has caused at least three times the ULN elevation of liver aminotransferases (ALT and AST) in about 11 percent of patients, accompanied by elevated bilirubin in a small number of cases, warranting serum aminotransferase monitoring. Rare cases of unexplained hepatic cirrhosis have been reported after prolonged use (>12 months) of bosentan in patients with multiple comorbidities on multiple drug therapies. There have also been rare reports of liver failure. Strict adherence to the monthly monitoring schedule for the duration of treatment is required to use bosentan. Bosentan is likely to cause major birth defects if used by pregnant females; therefore, it is considered a teratogenic substance. Due to the significant potential for fetal harm as well as the potential for serious liver damage, bosentan can only be accessed through the Tracleer Access Program (TAP) by calling 1-866-228-3546. Concomitant use of bosentan with cyclosporine A or with glyburide is contraindicated due to increased bosentan levels and increased liver enzymes, respectively.

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

Iloprost (Ventavis) and treprostinil (Tyvaso) have not been evaluated in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease) or with acute pulmonary infections. Such patients should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Both agents can cause symptomatic hypotension in patients with low systemic arterial pressure. Both agents inhibit platelet aggregation, so there may be an increased risk of bleeding, particularly among patients receiving anticoagulation.

Should signs of pulmonary edema occur when inhaled iloprost (Ventavis) is administered in patients with PH, the treatment should be stopped immediately. This may be a sign of pulmonary venous hypertension.

Treprostinil (Tyvaso) should be titrated slowly in patients with hepatic or renal insufficiency, because such patients will likely be exposed to greater systemic concentrations relative to patients with normal hepatic or renal function. Iloprost (Ventavis) has not been studied in patients with pulmonary hypertension and hepatic or renal impairment, both of which increase mean AUC in otherwise normal subjects.

**Drug Interactions:** <sup>38,39,40,41,42,43</sup>

Ambrisentan (Letairis) is metabolized by CYP450 3A, 2C19, uridine 5'-diphosphate glucuronosyltransferases (UGTs), 1A9S, 2B7S, and 1A3S. Ambrisentan is a substrate of the Organic Anion Transport Protein (OATP), and a substrate, but not an inhibitor, of P glycoprotein (P-gp). There are no known interactions where it is recommended to avoid concomitant use, but interactions with ritonavir, cyclosporine, and rifampin cannot be excluded due to their impact on the above enzymes/transporters.

Bosentan (Tracleer) is metabolized by and an inducer of CYP450 2C9 and 3A4, consequently plasma concentrations of drugs metabolized by these two isozymes will be decreased when bosentan is co-administered. Concomitant administration of both a CYP2C9 inhibitor (e.g., fluconazole or amiodarone) and a strong CYP3A inhibitor (e.g., ketoconazole, itraconazole) or a moderate CYP3A inhibitor (e.g., amprenavir, erythromycin, fluconazole, diltiazem) with bosentan will likely lead to large increases in plasma concentrations of bosentan and is therefore not recommended. The concomitant administration of bosentan and cyclosporine or glyburide is contraindicated. The dose of bosentan should be adjusted when initiating lopinavir/ritonavir or other ritonavir-containing regimens for HIV.

Sildenafil (Revatio) is metabolized through the CYP450 3A4 (major) and 2C9 (minor) isoenzyme systems. The use of sildenafil with ritonavir and other potent CYP3A inhibitors is not recommended.

Tadalafil is a substrate of and predominantly metabolized by CYP450 3A. In patients taking potent CYP3A inhibitors (e.g., ketoconazole, itraconazole), avoid concomitant use. The dose of ritonavir should be adjusted if given with tadalafil. Patients on chronic potent inducers of CYP3A (e.g., rifampin) should avoid tadalafil.

The concomitant use of PDE-5 inhibitors (sildenafil and tadalafil) with nitrates in any form is contraindicated. Also, there is a blood pressure lowering effect with concomitant PDE-5 inhibitor and alpha-blocker use.

Drug interaction studies have not been conducted with inhaled treprostinil (Tyvaso). However, there are some studies for the oral and SC formulations of treprostinil. Concomitant treprostinil (Tyvaso) with diuretics, antihypertensives or other vasodilators may increase the risk of systemic hypotension. Treprostinil (Tyvaso) dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. Do not mix treprostinil (Tyvaso) with other medications in the Optineb-ir device; compatibility of treprostinil with other medications has not been studied.

Although clinical studies have not been conducted, *in vitro* studies of iloprost (Ventavis) indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected. Concomitant iloprost (Ventavis) with antihypertensives or other vasodilators may increase the risk of systemic hypotension. Direct mixing of iloprost (Ventavis) with other medications in the I-neb<sup>®</sup> AAD<sup>®</sup> System or the Prodose<sup>®</sup> AAD<sup>®</sup> System has not been evaluated; therefore do not mix with other medications.

Both treprostinil (Tyvaso) and iloprost (Ventavis) inhibit platelet aggregation, so there may be an increased risk of bleeding, particularly among patients receiving anticoagulation.

**Adverse Effects**

Drug	Epistaxis	Head-ache	Dyspepsia	Flushing	Insomnia	Erythema	Elevations in ALT/AST (> 3X ULN)
<b>Oral Agents</b>							
ambrisentan (Letairis) <sup>44</sup>	nr	15 (14)	nr	4 (1)	nr	nr	0.8-2.8
bosentan (Tracleer) <sup>45</sup>	nr	22 (20)	4 (0)	9 (5)	nr	nr	11 (2)
sildenafil 20 mg three times daily (Revatio) <sup>46</sup> n=69 (placebo n=70)	9 (1)	46 (39)	13 (7)	10 (4)	7 (1)	6 (1)	nr
tadalafil 40 mg/day (Adcirca) <sup>47</sup> n=79 (placebo n=82)	nr	42 (15)	10 (2)	13 (2)	nr	nr	nr
<b>Inhalation Agents</b>							
Drug	Cough	Flushing	Headache	Trismus	Nausea	Syncope	Throat Irritation/Pharyngolaryngeal Pain
iloprost (Ventavis) <sup>48</sup> n=101 (placebo n=102)	39 (26)	27 (9)	30 (20)	12 (3)	13 (8)	8 (5)	nr
treprostinil (Tyvaso) <sup>49</sup> n=115 (placebo n=120)	54 (29)	15 (<1)	41 (23)	nr	19 (11)	7 (<1)	25 (14)

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

nr = not reported.

In post-marketing experience, there have been cases of sudden decrease or loss of hearing in temporal association with the use of PDE-5 inhibitors like sildenafil (Revatio) and tadalafil (Adcirca). Non-arteritic anterior ischemic optic neuropathy (NAION), a cause of decreased



vision including permanent loss of vision, has been reported in temporal association with the use of PDE-5 inhibitors, including sildenafil and tadalafil. It is not possible to determine whether these reported events are directly related to the use of the drug, to the patient's underlying risk factors, to a combination of these, or to other factors.<sup>50,51</sup> As with other PDE-5 inhibitors, there have been rare reports of priapism related to sildenafil and tadalafil therapy.<sup>52,53</sup>

Reduced sperm counts, which may impair a man's ability to father children, have been observed in patients taking endothelin receptor antagonists (ERAs).<sup>54,55</sup>

Decreases in hemoglobin and hematocrit have been reported with the use of endothelin receptor antagonists, including bosentan and ambrisentan. Therefore, hemoglobin levels should be monitored. Peripheral edema is a known clinical consequence of PAH, and worsening PAH is also a known effect of endothelin receptor antagonists, including bosentan and ambrisentan.

Serious adverse events reported with the use of inhaled iloprost (Ventavis) include congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, kidney failure, hemoptysis, and pneumonia.<sup>56</sup> Serious adverse events reported with the use of treprostinil (Tyvaso) include pneumonia and hemoptysis.<sup>57</sup>

### ***Special Populations***<sup>58,59,60,61,62,63</sup>

#### *Pediatrics*

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

#### *Pregnancy*

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

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

Iloprost (Ventavis) and treprostinil (Tyvaso) are categorized as Pregnancy Category C and B, respectively.

#### *Renal Impairment*

No dosage adjustments are recommended for ambrisentan (Letairis) in mild to moderate renal impairment. No dosage adjustments are required for bosentan (Tracleer) with renal impairment.

No dosage adjustments are recommended for sildenafil (Revatio) in renal impairment in patients with PAH. The dose of tadalafil (Adcirca) should be adjusted in mild to moderate impairment; it should be avoided in patients with severe renal impairment.

Iloprost (Ventavis) has not been evaluated in subjects with impaired renal function.

Hepatic Impairment

Ambrisentan (Letairis) is not recommended in patients with moderate to severe hepatic impairment. There is no information in mild hepatic insufficiency but exposure to ambrisentan may be increased. Bosentan (Tracleer) should be avoided in patients with PAH who have moderate to severe hepatic impairment (see Black Box Warning and dosage adjustment and monitoring instructions in the package insert).

On the basis of ERA randomized controlled trials, the incidence of elevated liver function tests (LFTs) > 3 x upper limit of normal (ULN) is about 11 percent with bosentan and about two percent with ambrisentan.<sup>64</sup> These numbers may not be comparable, as the patient populations in the studies varied.

No dosage adjustments are recommended for sildenafil (Revatio) in hepatically impaired patients with PAH. The dose of tadalafil (Adcirca) should be adjusted in mild to moderate hepatic impairment; it should be avoided in severe hepatic impairment.

Iloprost (Ventavis) has not been evaluated in subjects with impaired hepatic function a slow up titration is recommended when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Since iloprost elimination is reduced in hepatic insufficiency, consider increasing the dosing interval (e.g., three to four hours between doses based on the patient's response at the end of the dose interval), in patients with Child Pugh Class B or C hepatic impairment.

**Dosages**

Drug	Initial Dose	Maximum Daily Dose	How Supplied
<b>Oral Agents</b>			
ambrisentan (Letairis) <sup>65</sup>	5 mg once daily with or without food	10 mg once daily	5, 10 mg tablets
bosentan (Tracleer) <sup>66</sup>	62.5 mg twice daily for first four weeks	125 mg twice daily	62.5, 125 mg tablets
sildenafil (Revatio) <sup>67</sup>	Oral: 20 mg three times daily with or without food Injectable: 10 mg (12.5 mL) three times daily as IV bolus	Oral: 20 mg three times daily	20 mg tablet 10 mg (12.5 mL) single-use vial
tadalafil (Adcirca) <sup>68</sup>	40 mg once daily	40 mg once daily	20 mg tablet
<b>Inhalation Agents</b>			
iloprost (Ventavis) <sup>69</sup>	2.5 mcg/dose; if tolerated increase to 5 mcg/dose. Administer 6 to 9 times daily (dosing intervals 2 hours while awake according to individual need and tolerability).	45 mcg (or 5 mcg nine times daily)	10 mcg/mL (30 single use 1 ml ampules) and 20 mcg/mL (30 single use 1 mL ampules) oral inhalation solution
treprostinil (Tyvaso) <sup>70</sup>	18 mcg (or 3 inhalations) four times daily about 4 hours apart; if 3 inhalations are not tolerated reduce to 1-2 inhalations as tolerated	54 mcg (or 9 inhalations) four times daily.	2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL) oral inhalation solution

The initial and maintenance dose of bosentan (Tracleer) is 62.5 mg twice daily in patients with low body weight (<40 kg) and >12 years old.

Dividing the dose of tadalafil (Adcirca) over the course of the day is not recommended.

Sildenafil (Revatio) injection is for the continued treatment of patients with PAH who are currently prescribed oral Revatio and who are temporarily unable to take oral medication. The dose of Revatio injection does not need to be adjusted for body weight.

Both iloprost (Ventavis) and treprostinil (Tyvaso) should be used with their respective devices. They should not be orally ingested.

Iloprost (Ventavis) is intended to be inhaled using either of two pulmonary drug delivery devices: the I-neb<sup>®</sup> AAD<sup>®</sup> System or the Prodose<sup>®</sup> AAD<sup>®</sup> System. To avoid potential interruptions in drug delivery due to equipment malfunctions, the patient should have easy access to a back-up for both devices. The 20 mcg/mL concentration is intended for patients who are maintained at the 5

mcg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing. Transitioning patients to the 20 mcg/mL concentration using the I-neb<sup>®</sup> AAD<sup>®</sup> System will decrease treatment times. Direct mixing of iloprost with other medications in these delivery devices has not been evaluated.

Patients should be advised that iloprost (Ventavis) should be inhaled at intervals of not less than two hours and that the acute benefits may not last two hours. Thus, patients may want to adjust times of administration to cover planned activities.

Treprostinil (Tyvaso) must be used only with the Tyvaso Inhalation System. To avoid potential interruptions in drug delivery because of equipment malfunction, the manufacturer recommends patients should have access to a back-up Optineb-ir device. One ampule of treprostinil (Tyvaso) contains a sufficient volume of medication for all four treatment sessions in a single day.

## ***Clinical Trials***

### Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by the manufacturer. Search strategy included the use of ambrisentan, bosentan, sildenafil, tadalafil, inhalation iloprost, and inhalation treprostinil for FDA-approved indication of PAH. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

### sildenafil (Revatio) and placebo

In a randomized, double-blind, placebo-controlled study, 278 patients (277 randomized, one patient not treated) with symptomatic PAH received placebo or sildenafil (20, 40, or 80 mg) orally three times daily for 12 weeks.<sup>71</sup> The primary endpoint of distance walked in six minutes which increased 45 m (+13 percent), 46 m (+13.3 percent), and 50 m (+14.7 percent) for 20, 40, and 80 mg sildenafil groups, respectively ( $p \leq 0.001$ ). There was no change in the placebo group. Mean pulmonary artery pressure, World Health Organization (WHO) functional class, and the incidence of clinical worsening were also assessed, but the study was not powered to assess mortality. Mean pulmonary artery pressure decreased 2.1, 2.6, and 4.7 mm Hg in the 20 mg ( $p=0.04$ ), 40 mg ( $p=0.01$ ), and 80 mg ( $p<0.001$ ) sildenafil groups, respectively, compared to an increase of 0.6 mm Hg in placebo. The WHO functional class was improved in the sildenafil groups for the 20 mg, 40 mg, and 80 mg strengths ( $p=0.04$ ,  $p=0.01$ , and  $p<0.001$ , respectively). The incidence of clinical worsening did not differ significantly between sildenafil and placebo. Common adverse events included flushing, dyspepsia, and diarrhea in the treatment arm. A total of 222 patients entered a long-term extension study of sildenafil monotherapy and showed

a 51 m increase in distance walked in six minutes at one year. Study doses exceeded FDA labeled doses.

Improvements in exercise tolerance, cardiac index, and quality of life (QOL) were demonstrated in a randomized, double-blind, placebo-controlled, crossover design trial. The evaluation compared the efficacy of sildenafil 25 to 100 mg three times daily to placebo in patients with primary pulmonary hypertension (PPH) over 12 weeks.<sup>72</sup> The primary endpoint was the change in exercise time on treadmill using the Naughton protocol (a graded exercise evaluation treadmill stress test).<sup>73</sup> Exercise time increased by 44 percent from  $475 \pm 168$  seconds at the end of placebo phase to  $686 \pm 224$  seconds at the end of sildenafil phase ( $p \leq 0.0001$ ). Secondary endpoints of cardiac index improved from  $2.8 \pm 0.9$  L/m<sup>2</sup> to  $3.45 \pm 1.1$  L/m<sup>2</sup> ( $p \leq 0.0001$ ), whereas pulmonary artery systolic pressure decreased insignificantly from  $105.23 \pm 17.82$  mm Hg to  $98.5 \pm 24.38$  mm Hg. There was significant improvement in the dyspnea and fatigue components of the QOL questionnaire. During the placebo phase, one patient died, and another had syncope. There were no significant side effects with sildenafil.

In a randomized, double-blind, placebo-controlled study, 267 PAH (WHO functional class I-IV) patients [stabilized on intravenous (IV)] epoprostenol, were randomized to placebo or sildenafil (in a fixed titration starting from 20 mg, to 40 mg and then 80 mg, three times a day) when used in combination with IV epoprostenol.<sup>74</sup> The primary endpoint showed that there was a statistically significant greater increase in six-minute walk distance for sildenafil compared with placebo at week 16. The mean change from baseline at week 16 was 30 m for the sildenafil group compared with four m for the placebo group, giving an adjusted treatment difference of 26 m (95% CI, 10.8 to 41.2,  $p = 0.0009$ ). Patients in the placebo group were three times more likely to experience a clinical worsening event (death, lung transplantation, initiation of bosentan therapy, or clinical deterioration requiring a change in epoprostenol therapy), and sildenafil patients experienced a significant delay in time to clinical worsening compared to placebo ( $p = 0.0074$ ).

#### sildenafil (Revatio) and bosentan (Tracleer)

In a double-blind trial, 26 patients with PAH (WHO functional class III) were randomized to receive sildenafil 50 mg twice daily for four weeks then 50 mg three times daily or bosentan 62.5 mg twice daily for four weeks then 125 mg twice daily over 16 weeks. Intention-to-treat analysis showed no significant differences between the two treatment groups as both improved right ventricular (RV) mass, six-minute walk distance, and cardiac index.<sup>75</sup> Study doses of sildenafil exceeded FDA labeled doses.

#### bosentan (Tracleer) and placebo

The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was a 16-week, multicenter, randomized, double-blind, placebo-controlled study evaluating the effect of bosentan, a dual endothelin receptor antagonist, on systemic pulse oximetry (primary safety end point) and pulmonary vascular resistance (primary efficacy end point) in patients with World Health Organization functional class III Eisenmenger syndrome. Hemodynamics were assessed by right- and left-heart catheterization.<sup>76</sup> Eisenmenger syndrome is characterized by the development of pulmonary arterial hypertension with consequent intracardiac right-to-left shunt and hypoxemia in patients with preexisting congenital heart disease. Secondary end points included exercise capacity assessed by six-minute walk distance, additional hemodynamic parameters, functional capacity, and safety. Fifty-four patients were randomized 2:1 to bosentan ( $n = 37$ ) or placebo ( $n = 17$ ) for 16 weeks. The placebo-corrected effect on systemic pulse

oximetry was one percent (95% CI, -0.7 to 2.8), demonstrating that bosentan did not worsen oxygen saturation. Compared with placebo, bosentan reduced pulmonary vascular resistance index (-472 dyne.s.cm<sup>-5</sup>; p=0.0383). The mean pulmonary arterial pressure decreased (-5.5 mm Hg; p=0.0363), and the exercise capacity increased (53.1 m; p=0.0079). Four patients discontinued as a result of adverse events, two (five percent) in the bosentan group and two (12 percent) in the placebo group. Bosentan was well tolerated and improved exercise capacity and hemodynamics without compromising peripheral oxygen saturation.

The purpose of the study was to investigate the effects of bosentan (125 or 250 mg twice daily) on echocardiographic and Doppler variables in 85 patients with World Health Organization class III or IV PAH.<sup>77</sup> Patients had primary pulmonary hypertension (84 percent) or PAH associated with connective tissue disease. Of these, 29 patients received placebo and 56 received bosentan (1:2 randomization). Six-minute walk tests and echocardiograms were performed at baseline and after 16 weeks of treatment. Baseline characteristics were similar in the placebo and bosentan groups, and echocardiographic and Doppler findings were consistent with marked abnormalities of right ventricular (RV) and left ventricular (LV) structure and function that were due to PAH. The treatment effect on six-minute walking distance was 37 m in favor of bosentan (p=0.036). Treatment effects of bosentan compared with placebo on other parameters were statistically significant. Bosentan improved RV systolic function and LV early diastolic filling and lead to a decrease in RV dilation and an increase in LV size in patients with PAH.

The EARLY trial was a multicenter, double-blind, randomized, placebo-controlled trial of 185 patients with WHO class II PAH to assess the effectiveness of bosentan (n=93) versus placebo (n=92).<sup>78,79</sup> The primary endpoints were pulmonary vascular resistance (PVR) at month six (expressed as a percentage of baseline) and change from baseline in six-minute walk distance. Compared with placebo, bosentan treatment was associated with a reduced incidence of worsening of at least one functional class (three percent for bosentan versus 13 percent for placebo, p=0.03) and improvement in hemodynamic variables (including PVR, p<0.05). The +19 m mean (+14 m median) increase in six-minute walk distance with bosentan versus placebo was not significant (p=0.08). There was a significant delay in time to clinical worsening (first seen primarily as symptomatic progression of PAH) with bosentan compared with placebo (hazard ratio 0.2, p=0.01), however patients who had withdrawn for any reason were not included in the analysis. Serious adverse events (e.g., syncope, right ventricular failure) were reported in 12 of the patients in the bosentan group and eight in the placebo group. This study was funded by the manufacturer of bosentan.

A double-blind, placebo controlled trial randomized 213 patients with severe PAH to bosentan 62.5 mg or placebo, twice daily for four weeks, followed by either of two doses of bosentan (125 or 250 mg) twice daily for a minimum of 12 weeks.<sup>80</sup> At week 16, patients treated with bosentan had an improved six-minute walking distance (primary endpoint); the mean difference between the placebo group and the combined bosentan groups was 44 m (95 % CI, 21 to 67, p<0.001). Bosentan also improved the secondary endpoints of Borg dyspnea index and WHO functional class and increased the time to clinical worsening.

#### ambrisentan (Letairis) and placebo

ARIES-1 and ARIES-2 were two 12-week, randomized, double-blind, placebo-controlled, multicenter studies conducted in 393 patients with PAH (WHO Group I).<sup>81,82</sup> The study designs were identical with the exception of the comparative doses used (ARIES-1: ambrisentan 5 mg and 10 mg; ARIES-2: ambrisentan 2.5 mg and 5 mg) and the geographic locations. Both studies allowed the addition of ambrisentan or placebo to current therapy except epoprostenol,

treprostinil, iloprost, bosentan or sildenafil. The primary study endpoint was the six-minute walk distance. Both studies showed that active treatment with ambrisentan resulted in significant improvement in six-minute walk distance and improvements increased with dose ( $p < 0.001$ ). Additionally, time to clinical worsening was defined as the first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, study withdrawal due to the addition of other PAH therapeutic agents or study withdrawal due to early escape. Early escape is defined as any two of the following: a 20 percent decrease in the six-minute walk distance; an increase in WHO functional class; worsening right ventricular failure; rapidly progressing cardiogenic, hepatic, or renal failure; or refractory systolic hypotension. There was a significant delay in the time to clinical worsening for patients receiving ambrisentan versus placebo (ARIES-1: 97 versus 89 percent;  $p = 0.03$  and ARIES-2: 94 versus 79 percent;  $p = 0.005$ ).

Long-term follow-up of ARIES-1, ARIES-2, and ARIES-E (the open-label extension of these studies where 383 patients received ambrisentan 2.5, 5, or 10 mg) was performed.<sup>83</sup> After two years, mean change from baseline in six-minute walk distance was improved for the 5 mg (+23 m; 95% CI, 9 to 38 m) and 10 mg (+28 m; 95% CI, 11 to 45 m) groups. Estimates of survival and freedom from clinical worsening for the combined dose group were 94 percent and 83 percent, respectively, at one year and 88 percent and 72 percent, respectively, at two years. The annualized risk of aminotransferase abnormalities greater than 3 x the upper limit of normal (ULN) was approximately two percent per year. Ambrisentan was generally well tolerated.

#### bosentan (Tracleer) and ambrisentan (Letairis)

Due to a lack of other data on survival for agents in this class, this analysis has been included. A retrospective cohort analysis was conducted from two double-blind, randomized trials and their open-label extensions, treated with first-line bosentan, with a three year follow-up.<sup>84</sup> The results suggest that first-line bosentan therapy, followed by the addition of other disease-specific therapies as required, improve survival in patients with advanced PAH. Some uncontrolled observational studies suggest ambrisentan may be a once-daily alternative for patients who have experienced asymptomatic aminotransferase elevations on other endothelin receptor antagonists after aminotransferase levels have returned to normal.<sup>85,86</sup>

#### tadalafil (Adcirca) and placebo

Tadalafil was studied in a 16-week, double-blind, placebo-controlled trial of 405 patients with PAH and either treatment-naïve or on background therapy with bosentan (Tracleer).<sup>87,88</sup> Of the patients in the study, 53 percent were receiving concomitant bosentan therapy. Participants were randomized to placebo or tadalafil 2.5, 10, 20, or 40 mg orally once daily. The primary end point was the change from baseline to week 16 in the distance walked in six minutes. Secondary endpoints included: changes in World Health Organization (WHO) functional class, clinical worsening, and health-related quality of life. Tadalafil was found to increase the distance walked in six minutes. This effect was dose-dependent; only the 40-mg dose met the specified level of statistical significance ( $p < 0.01$ ). Overall, the mean placebo-corrected treatment effect was 33 m (95% CI, 15 to 50 m). The treatment effect was greater in the bosentan-naïve group, with an increase of 44 m (95% CI, 20 to 69 m) compared with 23 m (95% CI, -2 to 48 m) in patients on background bosentan therapy. Tadalafil 40 mg improved the time to clinical worsening ( $p = 0.041$ ), incidence of clinical worsening (68 percent relative risk reduction;  $p = 0.038$ ), and health-related quality of life. The changes in WHO functional class were not statistically significant.

### Iloprost (Ventavis) and placebo

A randomized, double-blind, multicenter, placebo-controlled trial of 203 patients with PAH and chronic thromboembolic PH, FC III or IV, were randomized to inhaled iloprost (2.5 to 5 mcg, six to nine times per day) or placebo for 12 weeks.<sup>89,90</sup> The primary endpoint was improvement of WHO class and greater than 10 percent improvement in six-minute walk test and was greater in the iloprost group versus placebo (17 versus five percent,  $p=0.0007$ ).

### Iloprost (Ventavis) and bosentan

In a randomized, multicenter, double-blind trial, inhaled iloprost (5 mcg) or placebo was added to stable monotherapy with bosentan for 12 weeks.<sup>91</sup> Efficacy endpoints included change from baseline in six-minute walk distance (six-MWD), modified New York Heart Association (NYHA) functional class, hemodynamic parameters, and time to clinical worsening. A total of 67 patients with PAH (55 percent IPAH, 45 percent associated PAH, 94 percent NYHA class III, and mean baseline six-MWD of 335 m) were randomized. At Week 12, patients receiving iloprost had a mean increase in six-MWD of 30 m ( $p=0.001$ ); placebo patients had a mean six-MWD increase of four m ( $p=0.69$ ), with a placebo-adjusted difference of +26 m ( $p=0.051$ ). NYHA status improved by one class in 34 percent of iloprost versus six percent in placebo ( $p=0.002$ ). Iloprost delayed the time to clinical worsening ( $p=0.0219$ ). Improvements were noted in post-inhalation placebo-adjusted change in mean pulmonary artery pressure (-8 mm Hg;  $p<0.001$ ) and pulmonary vascular resistance ( $p<0.001$ ). Combination therapy was well tolerated.

### treprostinil (Tyvaso) and placebo

TRIUMPH-1 was a randomized, double-blind, multicenter, 12-week placebo-controlled study of 235 patients with PAH (mostly functional class III) who were receiving either bosentan or sildenafil for at least three months prior to study initiation.<sup>92,93,94</sup> Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or treprostinil in four daily treatment sessions with a target dose of nine breaths (54 mcg) per session over the course of the 12-week study. Patients were predominantly female (82 percent); bosentan was the concomitant oral medication in 70 percent of those enrolled; sildenafil in 30 percent. Patients taking treprostinil in four daily inhalation sessions achieved a 20-meter improvement in six-minute walk distance over those taking placebo ( $p<0.0005$ ). The safety and effectiveness in patients with underlying lung disease has not been established.

### Meta-analysis

A meta-analysis of 21 randomized controlled PAH trials reported that therapy with a prostanoid, an ERA, or a PDE-5 inhibitor improves mortality compared to placebo (1.5 versus 3.8 percent, RR 0.57, 95% CI, 0.35-0.92).<sup>95</sup> The average duration of the trials was 14.3 weeks.

A systematic review and meta-analysis through November 2009 included 3,758 patients.<sup>96</sup> Data was pooled for three classes of medications: prostanoids, endothelin-receptor antagonists (ERAs), and phosphodiesterase type 5 (PDE5) inhibitors. Pooled relative risks (RRs) and 95% confidence intervals were calculated for mortality, six-minute walk distance, dyspnea scores, hemodynamic parameters, and adverse effects. Mortality in the control arms was a combined 4.2 percent over the mean study length of 14.9 weeks. There was significant mortality benefit with prostanoid treatment (RR 0.49, 95% CI, 0.29 to 0.82), particularly comparing intravenous



agents to control (RR 0.30, 95% CI, 0.14 to 0.63). Mortality benefit was not observed for ERAs (RR 0.58, 95% CI, 0.21 to 1.60) or PDE5 inhibitors (RR 0.30, 95% CI, 0.08 to 1.08). All three classes of medication improved other clinical and hemodynamic endpoints. Adverse effects that were increased in treatment arms include jaw pain, diarrhea, peripheral edema, headache, and nausea in prostanoids; and visual disturbance, dyspepsia, flushing, headache, and limb pain in PDE5 inhibitors. No adverse events were significantly associated with ERA treatment.

The pooled effect of a systematic review of all PAH clinical trials, produced a significant all-cause mortality reduction: 39 percent (95% CI, 2%-62%, p=0.041).<sup>97</sup> This reduction only applied to patients with advanced disease for 16 weeks. Individual drug classes did not produce a statistically significant reduction in all-cause mortality. Mechanism of mortality reduction unclear but not related to specific drug class, dose, or drug effects on six-minute walk distance, or hemodynamics.

### **Summary**

The treatment for pulmonary arterial hypertension (PAH) is challenging and complicated. Untreated PAH is characterized by a progressive increase in pulmonary arterial pressure, secondary right ventricular failure, and premature death.

According to the 4<sup>th</sup> World Symposium on PH, nonresponders to acute vasoreactivity testing or responders who remain in WHO FC III PAH are candidates for treatment with a PDE-5 inhibitor or an ERA. Among prostanoids, iloprost (Ventavis) and treprostinil (Tyvaso) can be administered by oral inhalation.

Recommendations for treatment of WHO FC II include the oral agents ambrisentan (Letairis), bosentan (Tracleer), sildenafil (Revatio) (Grade A for all) and tadalafil (Adcirca) (Grade B). Recommendations for WHO FC III include oral agents ambrisentan (Letairis), bosentan (Tracleer), sildenafil (Revatio), and inhaled iloprost (Ventavis) (Grade A for all) and tadalafil (Adcirca) (Grade B). Continuous IV epoprostenol, a synthetic prostacyclin, remains first-line for PAH FC IV due to its demonstrated survival benefit. Inhalation iloprost (Ventavis) is considered an alternative (Grade B). Tadalafil (Adcirca) and inhaled treprostinil (Tyvaso) were investigational at the time of the 4<sup>th</sup> World Symposium.

Both oral PDE-5 inhibitors sildenafil (Revatio) and tadalafil (Adcirca) improve exercise tolerance and hemodynamic status, as well as delay clinical worsening.

The oral endothelin receptor antagonists, bosentan (Tracleer) and ambrisentan (Letairis) have been shown to improve exercise capacity, hemodynamics, quality of life, and increase time to clinical worsening in short-term studies. Ambrisentan (Letairis) is approved in patients with WHO Functional Class II and Class III symptoms while bosentan (Tracleer) is approved in patients with Class II to Class IV symptoms.

The inhalation prostacyclin analogues, iloprost (Ventavis) are approved in FC III to IV and treprostinil (Tyvaso) for FC III. Iloprost (Ventavis) has improved exercise capacity and improvements in clinical symptoms and events. Treprostinil (Tyvaso) has shown to improve exercise capacity.

Drug selection is complex and depends on several factors including functional severity, route of administration, adverse events, patient preference, physician experience, and clinical judgment. Combination therapy should be considered for patients who do not improve with monotherapy.

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