# *Therapeutic Class Overview*
# *Pulmonary Arterial Hypertension Agents*

**Therapeutic Class**

- **Overview/Summary:** Pulmonary arterial hypertension (PAH) is characterized by elevated pulmonary arterial pressure and increased pulmonary vascular resistance leading to right heart failure. It's a life-threatening disease associated with a high mortality rate. Patients with PAH are assessed based on the World Health Organization (WHO) and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.[10] Four classes of drugs are Food and Drug Administration (FDA)-approved for the treatment of PAH, including prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[1-8] The prostanoids, iloprost (Ventavis®) and treprostinil (Tyvaso®), compensate for inadequate production of prostacyclin $I_2$ in PAH by causing vasodilatation and inhibiting platelet aggregation. Other prostanoid products are FDA-approved for the treatment of PAH; however they are only available for intravenous or subcutaneous administration and not included within this review.[1,6,12] The ERAs, ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®), competitively bind to endothelin receptors, $ET_A$ and $ET_B$, to counteract the vasoconstrictive effects of endothelin-1.[2,3,7] The PDE-5 inhibitors, sildenafil (Revatio®) and tadalafil (Adcirca®), increase the concentrations of cyclic guanosine monophosphate resulting in relaxation of pulmonary vascular bed.[4,5,12] Sildenafil and tadalafil are also indicated for erectile dysfunction under different trade names.[10] Currently, sildenafil tablets are available generically.[9] Riociguat (Adempas®) is the first agent within the novel class of soluble guanylate cyclase stimulators. It exerts its pharmacologic effect through the stimulation of the nitric oxide-soluble guanylate cyclase-cyclic guanosine monophosphate pathway, ultimately resulting in vasodilation.[8]

  Ambrisentan, bosentan and macitentan are contraindicated in women who are or may become pregnant. Bosentan is also not recommended in patients with liver impairment. Due to these serious contraindications, these drugs have black box warnings and can only be obtained through restricted distribution programs.[2,3,7] The PDE-5 inhibitors are contraindicated in patients using any form of organic nitrate.[4,5] Bosentan is metabolized by and is an inducer of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 and thus carries a risk of significant drug-drug interactions.[3] In August 2012, the prescribing information for sildenafil was updated with a warning stating that the use of sildenafil in pediatric patients is not recommended due to increased mortality associated with higher doses, and noted that lower doses are not effective in improving exercise capacity.[4]

**Table 1. Current Medications Available in Therapeutic Class[1-8,12]**

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Ambrisentan (Letairis®) | Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening* | Tablet:<br>5 mg<br>10 mg | - |
| Bosentan (Tracleer®) | Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening† | Tablet:<br>62.5 mg<br>125 mg | - |
| Iloprost (Ventavis®) | Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration‡ | Ampule for inhalation:<br>10 µg/mL<br>20 µg/mL | - |
| Macitentan (Opsumit®) | Treatment of PAH (WHO Group I) to delay disease progression‖# | Tablet:<br>10 mg | - |
| Riociguat (Adempas®) | Treatment of PAH (WHO Group I) to improve exercise ability, improve WHO functional class and delay clinical worsening and treatment of persistent/recurrent CTEPH after surgical | Tablet:<br>0.5 mg<br>1 mg<br>1.5 mg | - |

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | treatment or inoperable CTEPH to improve exercise capacity‖ | 2 mg<br>2.5 mg | |
| Sildenafil (Revatio®) | Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening§‖ | Tablet:<br>20 mg<br><br>Vial for injection:<br>0.8 mg/mL | ✔ |
| Tadalafil (Adcirca®) | Treatment of PAH (WHO Group I) to improve exercise ability¶ | Tablet:<br>20 mg | - |
| Treprostinil (Tyvaso®) | Treatment of PAH (WHO Group I) to improve exercise ability | Ampule for inhalation:<br>0.6 mg/mL | - |

CTEPH=Chronic Thromboembolic Pulmonary Hypertension, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization
*Studies establishing effectiveness included predominantly patients with World Health Organization (WHO) Functional Class II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64%) or PAH associated with connective tissue diseases (32%).
†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).
‡Studies establishing effectiveness included predominately patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%), PAH associated with connective tissue diseases (23%).
§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).
‖ Approved for use in adults only.
¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).
#Disease progression included death, initiation of intravenous or subcutaneous prostanoids or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).

**Evidence-based Medicine**

- Randomized controlled trials have demonstrated the efficacy of the oral pulmonary arterial hypertension agents in increasing exercise capacity and improving World Health Organization and New York Heart Association functional class; however, no head to head trials have been conducted.[15-40]
- Only small studies evaluating the effect of combination therapy have been conducted, and statistically significant improvements have not consistently been demonstrated.[10,22,33,34,38,40]
- Common adverse events in the prostanoids class are jaw pain, diarrhea, headache and flushing.[1,6,12] Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests.[2,3,7,12] The phosphodiesterase-5 inhibitors are generally well tolerated and common adverse effects include headache, flushing, and dyspepsia.[4,5,12] The most common adverse events associated with the soluble guanylate cyclase stimulators can be ascribed to the vasodilatory mechanism of action, including headache, dizziness, nausea and hypotension.[8]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
  - Oral calcium-channel blockers (CCB) are recommended only for patients with positive acute vasodilator response to testing.[10,11,14]
  - Oral therapy with either a phosphodiesterase-5 inhibitor or an endothelin receptor antagonist is recommended as first-line treatment in patients who are considered lower risk and are not candidates for CCBs.[10,11,14]
  - Intravenous epoprostenol is the preferred treatment in patients at higher risk and poor prognostic indexes and is the only therapy shown to prolong survival.[10]
  - Combination therapy should be considered when patients are not responding adequately to initial monotherapy.[10]

- Other Key Facts:
  - Ambrisentan, bosentan, macitentan and riociguat are distributed through a restricted distribution program and iloprost and treprostinil are distributed through specialty pharmacies.[1,2,3,6]
  - On March 4, 2011, the Food and Drug Administration removed a boxed warning regarding potential for liver injury from the prescribing information for ambrisentan based on the review of post-marketing data.[41]
  - Sildenafil tablets are the only oral pulmonary arterial hypertension agent that are available generically.[9]
  - In August 2012, the prescribing information for sildenafil was updated to include a warning against the use of sildenafil in pediatric patients. This was due to increased mortality seen in long-term clinical trials that included pediatric patients.[5]

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# *Therapeutic Class Review*
# *Pulmonary Arterial Hypertension Agents*

## Overview/Summary

The oral pulmonary hypertension agents are Food and Drug Administration (FDA)-approved for the treatment of patients with World Health Organization (WHO) Group I pulmonary arterial hypertension (PAH); however, there are differences in the study populations for which their FDA-approvals were based.[1-10] Typically, PAH is characterized by an elevated pulmonary arterial pressure and an increased pulmonary vascular resistance leading to right-sided heart failure. The prevalence of PAH is estimated to be 15 cases/million adults. The disease has a poor prognosis and an approximate mortality rate of 15% within one year on therapy.[10] The WHO classifies pulmonary hypertension into five groups. WHO Group I encompasses PAH, including idiopathic PAH, familial PAH, and PAH associated with connective tissue disorders, portal hypertension, human immunodeficiency virus infection, drugs and toxins and other disorders that affect the small pulmonary muscular arterioles. Patients with PAH are assessed based on the WHO and New York Heart Association (NYHA) functional classes that describe the disease severity from little (class I) to significant (class IV) impact on patient physical activity.[11]

Four classes of medications are currently FDA-approved for the treatment of WHO Group I PAH: prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[12] In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin $I_2$, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation.[10] The prostanoids act as vasodilators and platelet aggregation inhibitors. Currently, iloprost (Ventavis®) and treprostinil (Tyvaso®) inhaled formulations are the only prostanoids available orally; however, other products are available for intravenous or subcutaneous administration.[1,8] Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, $ET_A$ and $ET_B$.[2,3,10] Stimulation of $ET_A$ causes vasoconstriction and cell proliferation, while stimulation of $ET_B$ results in vasodilatation, antiproliferation and endothelin-1 clearance.[2,3] The ERAs, ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) competitively bind to both receptors with different affinities. Ambrisentan is highly selective for the $ET_A$ receptor, while bosentan is slightly more selective for the $ET_A$ receptor than the $ET_B$ receptor. Macitentan is associated with a high affinity and sustained occupancy of both ET receptors. However, the clinical significance of receptor affinities of the ERAs has not been established.[2,3] In patients with PAH there is also an impaired release of nitric oxide by the vascular endothelium thereby reducing cyclic guanosine monophosphate (cGMP) concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP.[10] The PDE-5 inhibitors, sildenafil (Revatio®) and tadalafil (Adcirca®), increase the concentrations of cGMP resulting in relaxation of pulmonary vascular bed.[4,5] In August 2012, the prescribing information for sildenafil was updated with a warning stating that the use of sildenafil in pediatric patients is not recommended due to increased mortality associated with higher doses, and noted that lower doses are not effective in improving exercise capacity.[4] Currently, sildenafil is the only oral PAH agent available generically.[9] Soluble guanylate cyclase (sGC) is an enzyme present in the cardiopulmonary system and is the receptor for nitric oxide. When bound to nitric oxide, sGC catalyzes synthesis of cGMP, which plays a role in the regulating processes that influence vascular tone, proliferation, fibrosis and inflammation. Riociguat (Adempas®) stimulation of this nitric oxide-sGC-cGMP pathway leads to increased generation of cGMP and thus, vasodilation.[8]

National and international consensus guidelines recommend oral therapy with either an ERA or a PDE-5 inhibitor as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.[10,13,14] Intravenous therapy with epoprostenol or treprostinil should be initiated as first-line treatment 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 that has demonstrated a prolonged survival benefit with its use.[10] Of note, epoprostenol is not currently available orally and is not included within this review. At the time the treatment guidelines were published, riociguat, inhaled treprostinil and oral tadalafil were not FDA-approved for the treatment of PAH.

## Medications

**Table 1. Medications Included Within Class Review[1-8]**

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| Ambrisentan (Letairis®) | Endothelin receptor antagonist | - |
| Bosentan (Tracleer®) | Endothelin receptor antagonist | - |
| Iloprost (Ventavis®) | Prostanoid | - |
| Macitentan (Opsumit®) | Endothelin receptor antagonist | - |
| Riociguat (Adempas®) | Soluble guanylate cyclase stimulator | - |
| Sildenafil (Revatio®) | Phosphodiesterase inhibitor | ✔ * |
| Tadalafil (Adcirca®) | Phosphodiesterase inhibitor | - |
| Treprostinil inhalation solution (Tyvaso®) | Prostanoid | - |

*Available generically in one dosage for or strength.

## Indications

**Table 2. Food and Drug Administration-Approved Indications[1-8]**

| Indication | Ambri-sentan | Bosentan | Iloprost | Macitentan | Riociguat | Sildenafil | Tadalafil | Treprostinil Inhalation Solution |
|---|---|---|---|---|---|---|---|---|
| Treatment of persistent/ recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity | | | | | ✔ ‖ | | | |
| Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening | ✔ * | ✔ † | | | | ✔ §‖ | | |
| Treatment of PAH (WHO Group I) to improve exercise ability | | | | | | | ✔ ¶ | ✔ |
| Treatment of PAH (WHO Group I) to delay disease progression | | | | ✔ ‖# | | | | |
| Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration | | | ✔ ‡ | | | | | |
| Treatment of PAH (WHO Group I) to improve exercise ability, improve WHO functional class and delay clinical worsening | | | | | ✔ ‖ | | | |

CTEPH=chronic thromboembolic pulmonary hypertension, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization
*Studies establishing effectiveness included predominantly patients with World Health Organization (WHO) Functional Class II to III symptoms and etiologies of idiopathic or heritable pulmonary arterial hypertension (PAH) (64%) or PAH associated with connective tissue diseases (32%).
†Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).
‡Studies establishing effectiveness included predominately patients with NYHA Functional Class III to IV symptoms and etiologies of idiopathic or heritable PAH (65%), PAH associated with connective tissue diseases (23%).
§Studies included predominately patients with NYHA class II or III symptoms and etiologies of primary pulmonary hypertension (71%) or pulmonary hypertension associated with connective tissue disease (25%).
‖ Approved for use in adults only.
#Disease progression included death, initiation of intravenous or subcutaneous prostanoids or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment).
¶Studies included predominately patients with NYHA class II or III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

## Pharmacokinetics

**Table 3. Pharmacokinetics[1-8,12]**

| Generic Name | Bioavailability (%) | Time to Peak Plasma Concentration | Excretion (%) | Metabolism (active metabolites) | Serum Half-Life (hours) |
|---|---|---|---|---|---|
| Ambrisentan | Unknown; not affected by food | 2 hours | Primarily non-renal; relative contributions not well established | Hepatic: CYP3A, CYP2C19; uridine 5'-diphosphate glucuronosyltrans-ferases-1A9S, 2B7S, and 1A3S (4-hydroxymethyl ambrisentan) | 9 |
| Bosentan | 50; not affected by food | 3 to 5 hours | Biliary; urine (<3) | Hepatic: CYP3A, CYP2C9 (Ro 48-5033) | 5 |
| Iloprost | Not reported | Not reported | Feces (12); urine (68) | Hepatic: β-oxidation (major), CYP450 (minor) (tetranor-iloprost) | 20 to 30 minutes |
| Macitentan | Unknown; not affected by food | 8 hours | Feces (24); urine (50) | Hepatic: CYP3A4 (major), CYP2C19 (minor) (ACT-132577) | 16 |
| Riociguat | 94; not affected by food | 1.5 hours | Feces (53); urine (40) | Hepatic: CYP1A1, CYP3A, CYP2C8, CYP2J2 (M1) | 12 (patients) 7 (healthy subjects) |
| Sildenafil | 41; high fat meal decreases absorption | 30 to 120 minutes (median, 60 minutes) | Feces (80); urine (13) | Hepatic: CYP3A4 (major) and CYP2C9 (minor) (N-desmethyl metabolite) | 4 |
| Tadalafil | Not reported; not affected by food | 2 to 8 hours (median, 4 hours) | Feces (61); urine (36) | Hepatic: CYP3A4 (none) | 15 (healthy); 35 (pulmonary hypertension, not on bosentan) |
| Treprostinil inhalation solution | 64 (18 µg); 72 (36 µg) | 0.25 and 0.12 hours | Feces (13); urine (79; 4 unchanged) | Hepatic: CYP2C8 (none) | 4 |

## Clinical Trials

The clinical trials demonstrating the safety and efficacy of the oral pulmonary arterial hypertension (PAH) agents are described in Table 4.[15-40]

The safety and efficacy of ambrisentan in the treatment of PAH was established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared ambrisentan to placebo in 394 patients. Compared to placebo, treatment with ambrisentan resulted in a significant increase in exercise capacity as measured by the six-minute walk distance (6MWD).[15] ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After one year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg ambrisentan groups (25, 28 and 37 m, respectively).

After two years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m).[17]

Bosentan was originally Food and Drug Administration (FDA)-approved in PAH patients with World Health Organization (WHO) functional class III and IV symptoms based on the results from two randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all bosentan groups compared to placebo. Bosentan was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO functional class symptoms.[20,21] The FDA-approved indication was subsequently expanded to include patients with WHO functional class II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with bosentan resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening function class symptoms in the bosentan group compared to placebo.[22]

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

The FDA-approval of macitentan in the treatment of PAH was based on a randomized, double-blind placebo-controlled trial (SERAPHIN) that evaluated the safety and efficacy of macitentan in patients with PAH at a dose of 3 or 10 mg once daily compared to placebo.[25] For the primary endpoint, 38.0, 31.4 and 46.4% of patients in the macitentan 3 mg, 10 mg and placebo groups, respectively, experienced an event over a median treatment period of 115 weeks. The most frequently observed event was worsening of PAH. At month six, the 6MWD decreased by a mean of 9.4 m in the placebo group, compared to placebo-corrected average increases of 16.8 and 22.0 m in the macitentan 3 and 10 mg groups, respectively. In addition, the WHO functional status improved from baseline in 13% of patients in the placebo group, compared to 20% of patients in the macitentan 3 mg group and 22% of patients in the macitentan 10 mg group.[25-27]

The FDA-approval of riociguat was based on two randomized, double-blind, placebo-controlled trials (CHEST-1 and PATIENT-1).[28,29] In the CHEST-1 study, the 6MWD increased from baseline by a mean of 39 m at week 16 in patients treated with riociguat compared to 6 m in the placebo group. Pulmonary vascular resistance decreased by 226 dyn•sec•cm–5 in the riociguat group compared to an increase of 23 dyn•sec•cm–5 in the placebo group.[28] In the PATIENT-1 study, the 6MWD increased from baseline by a mean of 30 m at week 12 in the riociguat 2.5 mg-maximum group compared to a decrease of 6 m in the placebo group. In addition, the pulmonary vascular resistance decreased by 223 dyn·sec·cm$^{-5}$ in the riociguat 2.5 mg-maximum group compared to 9 dyn·sec·cm$^{-5}$ in the placebo group.[29]

The safety and efficacy of sildenafil was evaluated in the SUPER-1 study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO functional class II or III symptoms. Compared to placebo, sildenafil significantly improved exercise capacity, as measured by the 6MWD, WHO functional class symptoms and hemodynamics.[30] In a three-year extension study (SUPER-2), 46% of patient increased 6MWD relative to SUPER-1 baseline, 18% decreased 6MWD from baseline 19% had died and 17% discontinued treatment or were lost to follow-up.[31] The addition of sildenafil to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO functional class II or III symptoms. Sildenafil added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo.[32]

Tadalafil was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO functional class II or III symptoms. Treatment with

tadalafil significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo.[34] In a 52-week extension trial, PHIRST-2, the improvements in 6MWD observed at the end of PHIRST appeared to be maintained through week 52 of PHIRST-2 (68 weeks total). In addition, 34% of patients enrolled in PHIRST-2 experienced an improvement in WHO functional class compared to baseline of the PHIRST trial.[35]

The FDA-approval of treprostinil solution for inhalation was based on the results of the TRIUMPH-1 trial, a randomized, double-blind, placebo-controlled study consisting of 235 patients. Nearly all patients had NYHA class III symptoms and all were receiving either bosentan or sildenafil for at least three months prior to study initiation. After 12 weeks of treatment, there was a significant increase in the 6MWD in the treprostinil group compared to placebo.[37] In a two-year extension study of patients completing TRIUMPH-1, improvements in 6MWD were maintained after six, 12, 18 and 24 months of treprostinil treatment ($P<0.05$ for all). The percentage of patients receiving treprostinil who were able to walk >440 m increased from 13% at baseline to 26% at 24 months ($P$ value not reported).[38]

**Table 4. Clinical Trials**

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Galie et al[15]<br>(ARIES-1 and 2)<br><br>Ambrisentan 5 or 10 mg daily<br><br>vs<br><br>placebo<br><br>(ARIES-2)<br><br>ambrisentan 2.5 or 5 mg daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT (1:1:1)<br><br>Patients (mean, 44 to 53 years of age) with PAH, idiopathic or associated with connective tissue disease, HIV infection, or anorexigen use | ARIES-1<br>N=202<br><br>ARIES-2<br>N=192<br><br>12 weeks | Primary:<br>Change from baseline in exercise capacity measured by 6MWD<br><br>Secondary:<br>Time to clinical worsening, change in WHO functional class, SF-36 Health Survey score, BDI, and BNP concentration | Primary:<br>There was a significant increase in 6MWD in all ambrisentan groups compared to placebo. The mean placebo-corrected 6MWD in ARIES-1 was 31 m (95% CI, 3 to 59; *P*=0.008) for ambrisentan 5 mg and 51 m (95% CI, 27 to 76; *P*<0.001) for ambrisentan 10 mg. In ARIES-2, the placebo-corrected 6MWD was 32 m (95% CI, 2 to 63; *P*=0.022) for ambrisentan 2.5 mg and 59 m (95% CI, 30 to 89; *P*<0.001) for ambrisentan 5 mg.<br><br>Secondary:<br>In ARIES-1, there was improvement in time to clinical worsening; however, it was not statistically significant compared to placebo in the 5, 10, and 5 and 10 mg combined groups (*P*=0.307, *P*=0.292, *P*=0.214, respectively). In ARIES-2, there was a significant improvement in time to clinical worsening in the 2.5, 5, and 2.5 and 5 mg combined groups compared to placebo (*P*=0.005, *P*=0.008, *P*<0.001, respectively).<br><br>In ARIES-1, the distribution of WHO functional class significantly improved in the ambrisentan group compared to placebo (*P*=0.036). In ARIES-2, the distribution of WHO functional class in the ambrisentan group improved, but it was not statistically significant compared to placebo (*P*=0.117).<br><br>In ARIES-1, there was an improvement in SF-36 scales, but it was not statistically significant compared to placebo (*P* value not reported). In ARIES-2, SF-36 scales significantly improved in the combined ambrisentan group compared to placebo (*P*=0.005).<br><br>There was a significant improvement in BDI 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 BDI compared to placebo for the 10 mg ambrisentan group in ARIES-1 (-0.9; 95% CI, -1.6 to -0.2; *P*=0.002), and for the 2.5 (-1.0; 95% CI, -1.9 to -0.2; *P*=0.046) and 5 mg (-1.2; 95% CI, -2.0 to -0.4; *P*=0.040) groups in ARIES-2.<br><br>There was a significant decrease in BNP concentrations compared to placebo in |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | the 5 and 10 mg groups in ARIES-1 and the 2.5 and 5 mg groups in ARIES-2 (*P*<0.003 in all groups).<br><br>Most adverse events were mild to moderate in severity and included peripheral edema, headache and nasal congestion. The proportion of patients who discontinued treatment due to adverse events was 3.0% in the placebo groups and 2.3% in the ambrisentan groups. |
| Badesch et al[16] (ARIES-3)<br><br>Ambrisentan 5 mg daily<br><br>Patients could receive background therapy with epoprostenol (intravenous), treprostinil (intravenous or subcutaneous) iloprost (inhaled) or sildenafil | OL<br><br>Patients ≥18 years of age with Group I, III, IV and V PAH with a total lung capacity ≥70% of predicted, $FEV_1$ ≥65% of predicted and a 6MWD of 150 to 450 m | N=224<br><br>24 weeks | Primary:<br>Change from baseline in 6MWD<br><br>Secondary:<br>Change in plasma BNP, BDI, WHO functional class, time to clinical worsening of PAH, survival and adverse events | Primary:<br>Treatment with ambrisentan was associated with a statistically significant increase in 6MWD at 24 weeks compared to baseline (21 m; 95% CI, 12 to 29; *P*<0.001).<br><br>Improvements in the 6MWD from baseline at 24 weeks were similar in Group I PAH patients receiving no background therapy (32 m; 95% CI, 17 to 48) compared to patients receiving background therapy with sildenafil alone (25 m; 95% CI, 11 to 40) or patients receiving background prostacyclin analog therapy with or without sildenafil (46 m; 95% CI, 7 to 85).<br><br>Secondary:<br>At week 24, ambrisentan treatment was associated with a statistically significant decrease in plasma BNP compared to baseline in the overall population (-26%; 95% CI, -34 to -16). Furthermore, a decrease was observed in most subgroups included within the study.<br><br>The WHO functional class improved in 23% of patients and deteriorated in 7% of patients (*P*<0.001). Dyspnea, as assessed by the BDI, decreased at 24 weeks compared to baseline (-0.5; 95% CI, -0.8 to -0.3).<br><br>At week 24, estimates for survival and freedom from clinical worsening of PAH were 97% (95% CI, 94 to 99) and 89% (95% CI, 84 to 93), respectively. The most frequent clinical worsening events reported were hospitalization for PAH, change of chronic sildenafil or prostacyclin analog therapy and death.<br><br>The most common treatment-related adverse events were peripheral edema, headache, dyspnea, upper respiratory tract infection, nasal congestion, fatigue, and nausea; however, discontinuation of ambrisentan treatment due to these |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | adverse events was infrequent.<br><br>Six patients (2.7%) experienced ALT/AST elevations greater than three times the upper limit of normal during the 24-week period. Four of the six patients had transient ALT/AST elevations less than five times the upper limit of normal and continued ambrisentan therapy with no additional events. Two patients had ALT/AST elevations greater than eight times the upper limit of normal and discontinued therapy. |
| Oudiz et al[17]<br>(ARIES-E)<br><br>Ambrisentan 2.5, 5, or 10 mg daily | ES, MC, OL<br><br>Patients (mean, 49 to 52 years of age) with PAH who completed ARIES-1 and ARIES-2 | N=350<br><br>Ongoing | Primary:<br>Change from baseline in exercise capacity measured by 6MWD, BDI, WHO functional class, long-term survival, and time to clinical worsening<br><br>Secondary:<br>Not reported | Primary:<br>After one year of treatment, there was an improvement in 6MWD of 25 m (95% CI, 5 to 45) for the 2.5 mg group, 28 m (95% CI, 14 to 42) for the 5 mg group, and 37 m (95% CI, 22 to 52) for the 10 mg group. After two years of treatment, improvements were sustained in the 5 (23 m; 95% CI, 9 to 38) and 10 mg (28 m; 95% CI, 11 to 45) groups, but not the 2.5 mg group (7 m; CI, -13 to 27).<br><br>After one year of treatment, there were improvements in BDI for the 5 (−0.59; 95% CI, -0.94 to -0.23) and 10 mg (-5.1; 95% CI, -1.00 to -0.03) groups, but not the 2.5 mg group (-0.08; 95% CI, -0.55 to 0.38). The trend continued after two years of treatments with changes in BDI from baseline of -0.33 (95% CI, -0.68 to 0.03) for the 5 mg, -0.60 (95% CI, -1.08 to -0.11) for the 10 mg, and 0.23 (95% CI, -0.31 to 0.76) for the 2.5 mg groups.<br><br>WHO functional class was either improved or maintained in 79 to 89% of patients.<br><br>The survival estimate for the overall population was 94% (95% CI, 91 to 96) at one year and 88% (95% CI, 83 to 91) at two years.<br><br>After one year, 83% (95% CI, 79 to 87) of the overall population was free from clinical worsening and 72% (95% CI, 67 to 76) were free from clinical worsening after two years.<br><br>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. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Secondary:<br>Not reported |
| Fox et al (abstract)[18]<br><br>Ambrisentan (dose and frequency not reported)<br><br>vs<br><br>bosentan (dose and frequency not reported) | RETRO<br><br>Patients with PAH requiring a switch from sitaxsentan to ambrisentan or bosentan following removal of sitaxsentan from the market | N=30<br><br>4 months | Primary:<br>Right atrial pressure, mean pulmonary artery pressure, pulmonary artery wedge pressures, cardiac output, PVR, BNP and WHO functional class changes<br><br>Secondary:<br>Not reported | Primary:<br>There were no significant change observed between either group with regard to changes in right atrial, mean pulmonary artery, and pulmonary artery wedge pressures, or in cardiac output, PVR, or BNP levels (*P* values not reported).<br><br>There was no change in WHO functional class between the groups. Four ambrisentan and two bosentan-treated patients reported fluid retention, and three bosentan-treated patients experienced an elevation of hepatic transaminases. Two of the patients had a right atrial pressure increase ≥5 mm Hg, and four had pulmonary artery wedge pressure increase ≥5 mm Hg (*P* values not reported).<br><br>Secondary:<br>Not reported |
| Yoshida et al[19]<br><br>Ambrisentan 5 or 10 mg daily | ES, MC, OL<br><br>Patients ≥18 years of age with a diagnosis of WHO Group I PAH (i.e., idiopathic PAH, familial PAH, or PAH related to other diseases such as collagen vascular diseases and congenital systemic-to-pulmonary shunts) | N=21<br><br>3 years | Primary:<br>Safety and tolerability<br><br>Secondary:<br>Change in 6MWD, WHO functional class, BDI, plasma BNP and hemodynamics | Primary:<br>Adverse events occurred in 100% of patients during the study period. The most common were nasopharyngitis (86%), pyrexia (38%), back pain (33%), cough (24%) and diarrhea (24%). Most adverse events were mild (57%) or moderate (24%) in severity. Four patients (19%) experienced severe adverse events including hemoptysis (one patient), subdural hematoma (one patient), dehydration and hepatic encephalopathy (one patient each), and pneumonitis and pulmonary congestion (one patient each). All severe adverse events were judged to be serious adverse events, and all except for the case of hemoptysis were not considered to be related to the study drug.<br><br>During the study period, an adverse event that was considered to be related to study drug occurred in 11 patients (52%). The adverse events occurring in three or more patients were epistaxis and hemoptysis. One patient had an ALT level (110 IU/L) greater than three times the upper limit of normal and a total bilirubin level 37.62 IU/L, which was greater than 1.5 times the upper limit of normal. In addition, AST and ALP levels were elevated.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | A statistically significant improvement in 6MWD occurred at week 24 (53.6 m; 95% CI, 29.4 to 77.7), week 36, (51.9 m; 95% CI, 24.1 to 79.7), week 48 (59.6 m; 95% CI, 35.3 to 83.9) and week 108 (56.4 m; 95% CI, 25.8 to 86.9) and week 156 (49.2 m; 95% CI, 13.5 to 84.9).<br><br>The WHO functional class was improved in 48% (10/21) of patients after 24 weeks of treatment, in 52% (11/21) after 48 weeks, in 47% (9/19) after 108 weeks and in 33% (2/6) after 156 weeks.<br><br>At 24 weeks, BDI had decreased from baseline (-0.8; 95% CI, -1.5 to 0.0). From week 132 on, the values varied considerably due to the small number of patients, but the decrease from baseline was maintained at week 24 onward.<br><br>After 24 weeks of treatment, the mean change from baseline in BNP was -109.5 ng/L. Throughout the remainder of the study, changes in BNP varied considerably but remained lower compared to baseline values (*P* value not reported).<br><br>The mean change from baseline in pulmonary arterial pressure was -8.2 mm Hg at week 36, -7.1 mm Hg at week 48, and from -13.9 to -5.4 mm Hg from week 60 onward (*P* values not reported).<br><br>The mean change from baseline in cardiac output was 0.29 L/minute at week 36 of study treatment and 0.23 L/minute at week 48. At week 60 and later, the mean change ranged from 0.00 to 0.46 L/minute and varied considerably (*P* values not reported). |
| Channick et al[20]<br><br>Bosentan 62.5 mg twice daily for four weeks, then 125 mg twice daily<br><br>vs<br><br>placebo | DB, MC, PC, RCT (2:1)<br><br>Patients (mean, 47 to 52 years of age) with symptomatic, severe primary pulmonary hypertension or | N=32<br><br>12 weeks | Primary:<br>Exercise capacity measured by 6MWD<br><br>Secondary:<br>Changes from baseline in cardiopulmonary hemodynamics, | Primary:<br>The 6MWD significantly increased from baseline in the bosentan group by 70 m (*P*<0.05) and decreased in the placebo group by 6 m (*P* value not reported). The mean change in 6MWD was 76 m (95% CI, 12 to 139; *P*=0.021) further for the bosentan group compared to the placebo group.<br><br>Secondary:<br>The bosentan group had significantly improved cardiopulmonary hemodynamics compared to the placebo group. The PVR, mean pulmonary artery pressure, pulmonary capillary wedge pressure and mean right arterial pressure all |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | pulmonary hypertension due to scleroderma (WHO functional class III to IV), despite previous treatment with vasodilators, anticoagulants, diuretics, cardiac glycosides, or supplemental oxygen | | BDI, WHO functional class, and withdrawal due to clinical worsening | significantly decreased compared to placebo with mean differences of -415 dynes/sec/cm$^{-5}$ (95% CI, -608 to -221; *P*<0.0002), -6.7 mm Hg (95% CI, -11.9 to -1.5; *P*=0.013), -3.8 mm Hg (95% CI, -7.3 to -0.3; *P*=0.035) and -6.2 (95% CI, -9.6 to -2.7; *P*=0.001), respectively. Cardiac index was significantly greater in the bosentan group compared to the placebo group with a mean difference of 1.0 L/min/m$^2$ (95% CI, 0.6 to 1.4; *P*<0.0001).<br><br>At week 12, the BDI was 1.6 (95% CI, 0.0 to 3.1; *P* value not reported) lower in the bosentan group compared to the placebo group.<br><br>At baseline, all patients in the study population were in WHO functional class III. After 12 weeks of therapy, 43% of patients improved to WHO functional class II and 57% of patients remained in WHO functional class III in the bosentan group (*P*=0.0039). In the placebo group, 9% of patients improved to WHO functional class II, 73% remained in WHO functional class III and 18% worsened to WHO functional class IV (*P*=1.0000). Overall, bosentan significantly improved WHO functional class compared to placebo (*P*=0.019).<br><br>The time to clinical worsening was significantly increased in the bosentan group compared to the placebo group (*P*=0.033) with three withdrawals in the placebo group and none in the bosentan group.<br><br>Adverse events in both the placebo and bosentan groups were similar with the exception of an asymptomatic increase in hepatic aminotransferases in two patients in the bosentan group, which returned to normal without discontinuation of the study drug. |
| Rubin et al[21] (BREATHE-1)<br><br>Bosentan 62.5 mg twice daily for four weeks, then 125 or 250 mg twice daily for 12 weeks<br><br>vs | DB, MC, PC, RCT<br><br>Patients (mean, 47 to 50 years of age) with symptomatic, severe primary pulmonary hypertension or | N=213<br><br>16 weeks | Primary:<br>Change from baseline in 6MWD<br><br>Secondary:<br>Changes from baseline in BDI, WHO functional class, and the | Primary:<br>After 16 weeks, there was 36 m increase in 6MWD 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).<br><br>Secondary:<br>After 16 weeks, the BDI decreased by a mean of -0.1±0.2 in the 125 mg group and -0.6±0.2 in the 250 mg group compared to a mean increase of 0.3±0.2 in the placebo group. The mean treatment effect favored bosentan by -0.6 (95% CI, -1.2 to -0.1). The placebo-corrected improvement was greater for the 250 mg |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| placebo | pulmonary hypertension due to connective-tissue disease (WHO functional class III or IV) despite treatment with anticoagulants vasodilators, diuretics, cardiac glycosides, or supplemental oxygen | | time to clinical worsening | group (-0.9; *P*=0.012) compared to the 125 mg group (-0.4; *P*=0.42).<br><br>At week 16, 38% of patients in the 125 mg group, 34% of patients in the 250 mg group, and 28% of patients in the placebo group had improved to WHO functional class II, while 3% of patients in the 125 mg group, 1% of patients in the 250 mg group and 0% of patients in placebo group had improved to WHO functional class I. Overall, there was a mean treatment effect of 12% favoring bosentan (95% CI, −3 to 25).<br><br>After 16 weeks, bosentan significantly increased the time to clinical worsening compared to placebo (*P*=0.004). |
| Galie et al[22] (EARLY)<br><br>Bosentan 62.5 mg twice daily for four weeks, then 125 mg twice daily (or 62.5 mg twice daily if weight <40 kg)<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT (1:1)<br><br>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 <2 cm in diameter, ventricular septal defect <1 cm in diameter, patent ductus arteriosus, or connective tissue or auto-immune | N=185<br><br>6 months | Primary:<br>Change from baseline in PVR and 6MWD<br><br>Secondary:<br>Time to clinical worsening and change from baseline in WHO functional class, BDI, total pulmonary resistance, mean pulmonary arterial pressure, cardiac index, and mixed venous oxygen saturation | Primary:<br>At six months, the bosentan group had a mean PVR that was 83.2% (95% CI, 73.8 to 93.7) of the baseline value compared to 107.5% (95% CI, 97.6 to 118.4) of the baseline value in the placebo group for a treatment effect of -22.6% (95% CI, -33.5 to -10.0; *P*<0.0001) favoring bosentan.<br><br>At six months, the mean 6MWD increased in the bosentan group by 11.2 m (95% CI, -4.6 to 27.0) and decreased in the placebo group by 7.9 m (95% CI, -24.3 to 8.5). The treatment effect of 19.1 (95% CI, -3.6 to 41.8; *P*=0.0758) favored bosentan, yet was not statistically significant.<br><br>Secondary:<br>There was a significant delay in time to clinical worsening with the bosentan group compared to the placebo group (HR, 0.227; 95% CI, 0.065 to 0.798; *P*=0.0114).<br><br>At six months, there was a significantly lower incidence of worsening WHO functional class in the bosentan group compared to the placebo group (3.4 vs 13.2%; *P*=0.0285). There were no significant differences seen in BDI with a mean treatment effect of -0.4 (95% CI, -1.0 to 0.1; *P*=0.2599). There were no significant differences seen in right atrial pressure with a mean treatment effect of -0.6 (95% CI, -2.0 to 0.9; *P*=0.662). Pulmonary artery pressure was |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | diseases | | | significantly lower in the bosentan group with a treatment effect favoring bosentan of -5.7 mm Hg (95% CI, -10.4 to -0.9; *P*<0.0001). Cardiac index and mixed venous oxygen saturation were significantly higher in the bosentan group compared to the placebo group with a mean treatment effect favoring bosentan of 0.24 L/min/$m^2$ (95 % CI, 0.02 to 0.45; *P*=0.025) and 4.8% (95% CI, 1.9 to 7.6; *P*=0.002), respectively.<br><br>Adverse events were similar in the placebo and bosentan groups. The most common adverse events in the bosentan group were nasopharyngitis and abnormal liver function tests. |
| McLaughlin et al[23]<br><br>Bosentan 125 mg twice daily plus iloprost 5 µg inhaled six to nine times daily<br><br>vs<br><br>bosentan 125 mg twice daily plus placebo | DB, MC, PC, RCT<br><br>Patients 10 to 80 years of age with symptomatic PAH receiving bosentan for ≥4 months with a 6MWD 100 to 425 m, resting mean pulmonary artery pressure >25 mm Hg, pulmonary capillary wedge pressure <15 mm Hg, and PVR ≥ 240 dyn/sec/$cm^{-5}$ | N=67<br><br>12 weeks | Primary:<br>Change from baseline in 6MWD, NYHA functional class, BDI and hemodynamic parameters<br><br>Secondary:<br>Not reported | Primary:<br>At 12 weeks, the post inhalation mean increase in 6MWD from baseline was 30 m for patients receiving iloprost (*P*=0.001) compared to 4 m in placebo-treated patients (*P*=0.69), with a placebo-adjusted difference of 26 m (*P*=0.051).<br><br>The BDI at 12 weeks was significantly improved in the iloprost group compared to baseline (*P*=0.031); however, the treatment effect compared to placebo was not statistically significant (*P*=0.16).<br><br>The NYHA class improved in 34% of patients receiving iloprost compared to 6% of placebo-treated patients compared to baseline (*P*=0.002).<br><br>The time to clinical worsening was significantly longer in iloprost-treated patients compared to those receiving placebo in patients on background bosentan therapy (*P*=0.0219).<br><br>A significant treatment effect was noted with iloprost compared to placebo in mean pulmonary artery pressure (-6 vs 2 mm Hg, respectively; *P*<0.001) and PVR (-164 vs -81 dyn/sec/$cm^{-5}$, respectively; *P*=0.007).<br><br>Secondary:<br>Not reported |
| Olschewski et al[24]<br><br>Iloprost 5 or 10 µg six to nine times daily | MC, PC, RCT<br><br>Patients (mean, 51 to 52 years of | N=203<br><br>12 weeks | Primary:<br>Clinical response as a composite of at least 10% in | Primary:<br>There was a significant treatment effect in favor of iloprost (OR, 3.97; 95% CI, 1.47 to 10.75; *P*=0.007). In a secondary analysis of the primary endpoint, only treatment assignment, and not demographic data or baseline characteristics, |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>placebo | age) with NYHA class III or IV primary or selected non-primary PAH (i.e., appetite-suppressant-associated, scleroderma-associated, or inoperable chronic thromboembolic PAH) despite use of conventional therapy (anticoagulants, diuretics, digitalis, calcium-channel blockers and supplemental oxygen) | | 6MWD, improvement in NYHA functional class in the absence of deterioration in clinical condition or death<br><br>Secondary: Changes in 6MWD, NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, the quality of life, clinical deterioration, death, and the need for transplantation | contributed significantly to the probability of response (*P*=0.01).<br><br>Secondary:<br>The percentage of patients with an increase of at least 10% in 6MWD was higher in the iloprost group; however, the difference was not significant (*P*=0.06). The absolute change in 6MWD was significantly higher by 36.4 m in the iloprost group compared to the placebo group (*P*=0.004).<br><br>Significantly more patients in the iloprost group had improvement in NYHA functional class compared to the placebo group (*P*=0.03). There was no significant difference between the groups in the percentage of patients with deterioration in NYHA functional class.<br><br>The mean Mahler Dyspnea Index score was significantly improved in the iloprost group compared to the placebo group (change, 1.42±2.59 vs 0.30±2.45; *P*<0.015).<br><br>Significant decreases in cardiac output (*P*<0.001), systemic arterial oxygen saturation (*P*<0.05) and mixed venous oxygen saturation (*P*<0.001) as well as significant increases in PVR (*P*<0.05) and right atrial pressure were observed in the placebo group vs baseline. Prior to the first inhalation of the day, there were no significant differences from baseline in the iloprost group. However after inhalation, significant decreases in pulmonary artery pressure (*P*<0.001), PVR (*P*<0.001), systemic arterial pressure (*P*<0.01) and systemic arterial oxygen saturation (*P*<0.05) as well as significant increases in cardiac output (*P*<0.001) and pulmonary artery wedge pressure (*P*<0.01) were observed.<br><br>The mean score on the EuroQol VAS improved significantly in the iloprost group (46.9±15.9 to 52.8±19.1) and decreased in the placebo group (48.6±16.9 to 47.4±21.1; *P*=0.026).<br><br>During the study one patient died in the iloprost group compared to four patients in the placebo group (*P*=0.37). In the iloprost group, 4.9% of patients met the criteria for clinical deterioration compared to 8.8% of patients in the placebo group (*P*=0.41). Overall, fewer patients died or deteriorated in the iloprost group than in the placebo group (4.9 vs 11.8%; *P*=0.09); however, the difference was |

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| | | | | not statistically significant.<br><br>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. |
| Pulido et al[25]<br>SERAPHIN<br><br>Macitentan 3 mg daily<br><br>vs<br><br>macitentan 10 mg daily<br><br>vs<br><br>placebo | DB, ED, MC, PC, RCT<br><br>Patients ≥12 years old with idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection or drug use or toxin exposure, a 6MWD of 50 m or more and WHO-FC class II, III or IV status | N=742<br><br>Duration varied | Primary:<br>Time from initiation of treatment to the first event related to PAH or death from any cause up to the end of treatment<br><br>Secondary:<br>Change in 6MWD from baseline to month six, percentage of patients with an improvement in WHO-FC at month six, death or hospitalization due to PAH up to the end of treatment, death from any cause up to the end of treatment and up to the end of the study and safety | Primary:<br>Over a median treatment period of 115 weeks, 38.0, 31.4 and 46.4% of patients in the macitentan 3 mg, 10 mg and placebo groups, respectively, experienced a PAH-related event or death from any cause (HR, 0.70; 97.5% CI, 0.52 to 0.96; *P*=0.01 for macitentan 3 mg vs placebo and HR, 0.55; 97.5% CI, 0.39 to 0.76; *P*<0.001 for macitentan 10 mg vs placebo).<br><br>Worsening of PAH was the most commonly observed event, occurring more frequently in the placebo group compared to either macitentan treatment arm (HR, 0.70; 97.5% CI, 0.52 to 0.96; *P*=0.01 for macitentan 3 mg vs placebo and HR, 0.55; 97.5% CI, 0.39 to 0.76; *P*<0.001 for macitentan 10 mg vs placebo).<br><br>Secondary:<br>At month six, the 6MWD decreased by a mean of 9.4 m in the placebo group, compared to placebo-corrected average increases of 16.8 m and 22 m in the macitentan 3 and 10 mg groups, respectively (97.5% CI, -2.7 to 36.4; *P*=0.01 for macitentan 3 mg vs placebo and 97.5% CI, 3.2 to 40.8, *P*=0.008 for macitentan 10 mg vs placebo).<br><br>Improvements from baseline to month six in the WHO-FC were observed in 13% of patients in the placebo group compared to 20% of patients in the macitentan 3 mg group and 22% of patients in the macitentan 10 mg group (*P*=0.006 and *P*=0.04, respectively).<br><br>Death or hospitalization due to PAH occurred in 26.0%, 20.7% and 33.6% of patients in the macitentan 3 mg, macitentan 10 mg and placebo groups, respectively (HR, 0.67; 97.5% CI, 0.46 to 0.97; *P*=0.01 for macitentan 3 mg vs placebo and HR, 0.50; 97.5% CI, 0.34 to 0.75; *P*<0.001 for macitentan 10 mg vs placebo).<br><br>There was no statistically significant difference in death from any cause up to the |

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| | | | | end of treatment in either treatment arm compared to placebo.<br><br>In terms of safety, 96.0, 94.6 and 96.4% of patients in the macitentan 3 mg, macitentan 10 mg and placebo groups, respectively, experienced ≥1 adverse events.<br><br>Adverse events resulting in treatment discontinuation occurred in 13.6, 10.7 and 12.4% of patients in the macitentan 3 mg, macitentan 10 mg and placebo groups, respectively. |
| Channick et al[26]<br>SERAPHIN subanalysis<br><br>Macitentan 3 mg daily<br><br>vs<br><br>macitentan 10 mg daily<br><br>vs<br><br>placebo | DB, ED, MC, PC, RCT<br><br>Patients ≥12 years old with idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection or drug use or toxin exposure, a 6MWD of 50 m or more and in class II, III or IV according to WHO-FC | N=742<br><br>Duration varied | Primary:<br>Time to death due to PAH or hospitalization for PAH up to the end of treatment and time to hospitalization for PAH up to the end of treatment<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with macitentan 3 and 10 mg resulted in reductions in the risk of death due to PAH or hospitalization for PAH by 33 and 50%, respectively, when compared to placebo (HR, 0.67; 97.5% CI, 0.46 to 0.97; *P*=0.0146 for macitentan 3 mg vs placebo and HR, 0.50; 97.5% CI, 0.33 to 0.75; *P*<0.0001 for macitentan 10 mg vs placebo).<br><br>The risk of hospitalization for PAH was reduced by 39 and 50% in the macitentan 3 and 10 mg groups, respectively (HR, 0.61; 97.5% CI, 0.42 to 0.90; *P*=0.0040 for macitentan 3 mg and HR, 0.50; 97.5% CI, 0.34 to 0.76; *P*=0.0001 for macitentan 10 mg).<br><br>Secondary:<br>Not reported |
| Mehta et al[27]<br>SERAPHIN subanalysis<br><br>Macitentan 3 mg daily | DB, ED, MC, PC, RCT<br><br>Patients ≥12 years old who | N=742<br><br>Duration varied | Primary:<br>Change in HRQoL and time to first occurrence of a | Primary:<br>Treatment with both the 3 and 5 mg doses of macitentan resulted in an improvement in mean HRQoL scores from baseline to month six.<br><br>Significant improvements compared to placebo were observed in the PCS and |

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| vs<br><br>macitentan 10 mg daily<br><br>vs<br><br>placebo | have idiopathic or heritable PAH or PAH related to connective-tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection or drug use or toxin exposure, a 6MWD of 50 m or more and in class II, III or IV according to WHO-FC | | ≥5 point decrease from baseline in PCS and MCS scores of Short Form 36-item over the entire treatment duration<br><br>Secondary:<br>Not reported | MCS scores in seven out of eight domains ($P$<0.05 for all domains except general health perception). Treatment with either dose of macitentan resulted in a reduction in risk of deterioration of HRQoL scores, as measured by time to first occurrence of a ≥5 point decrease in the PCS score (HR 0.70; 95% CI, 0.54 to 0.92; $P$=0.008 for macitentan 3 mg vs placebo and HR 0.65; 95% CI, 0.50 to 0.85; $P$=0.001 for macitentan 10 mg vs placebo) and the MCS score (HR 0.81; 95% CI, 0.63 to 1.03; $P$=0.085 for macitentan 3 mg vs placebo and HR 0.79, 95% CI, 0.61 to 1.01; $P$=0.053 for macitentan 10 mg vs placebo) across the study duration.<br><br>Secondary:<br>Not reported |
| Ghofrani et al[28]<br><br>CHEST-1<br><br>Riociguat titrated up to 2.5 mg three times daily<br><br>vs<br><br>placebo<br><br>All patients in the riociguat group were initiated at 1 mg three times daily and dose was titrated every two weeks based on patient's systolic blood pressure and signs or | DB, MC, PC, RCT<br><br>Patients 18 to 80 years of age with chronic thromboembolic pulmonary hypertension that was adjudicated to be technically inoperable or if they had persistent or recurrent pulmonary hypertension after undergoing pulmonary | N=261<br><br>16 weeks | Primary:<br>Change from baseline to end of week 16 in the 6MW distance<br><br>Secondary:<br>Changes from baseline to the end of week 16 in pulmonary vascular resistance, NT-proBNP level, WHO functional class, clinical worsening, Borg dyspnea score, the score on the | Primary:<br>At week 16, the 6MW distance had increased from baseline by a mean of 39 m in the riociguat group as compared to a mean decrease of 6 m in the placebo group (least-squares mean difference, 46 m; 95% CI, 25 to 67; $P$<0.001).<br><br>Secondary:<br>Pulmonary vascular resistance decreased by 226 dyn·sec·cm$^{-5}$ in the riociguat group, as compared to an increase of 23 dyn·sec·cm$^{-5}$ in the placebo group (least-squares mean difference, -246 dyn·sec·cm$^{-5}$; 95% CI, -303 to -190; $P$<0.001). Levels of NT-proBNP were significantly reduced in patients treated with riociguat ($P$<0.001) and changes in WHO functional class at 16 weeks also significantly favored the riociguat group ($P$=0.003) compared to placebo. There was no significant difference in the incidence of clinical worsening events between the riociguat and placebo groups (2 and 6%, respectively; $P$=0.17). The Borg dyspnea score decrease by 0.8 points in the riociguat group and increased by 0.2 points in the placebo group ($P$=0.004). There was a nominally significant difference between the two groups in the change in the EQ-5D score ($P$<0.001) but not in the LPH questionnaire score ($P$=0.1). |

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| symptoms of hypotension. | endarterectomy | | EQ-5D questionnaire, the score on the LPH questionnaire and adverse events | The most frequently occurring serious adverse events were right ventricular failure (3% in each group), syncope (2% in the riociguat and 3% in the placebo group) and hemoptysis (2% in the riociguat group). Drug-related serious adverse events in the 2.5-mg maximum group included three cases of syncope (1%) and single cases of increased hepatic enzyme levels, dizziness, presyncope, acute renal failure and hypotension (0.4% total). |
| Ghofrani et al[29]<br><br>PATENT-1<br><br>Riociguat in doses individually adjusted for each patient up to 2.5 mg three times daily<br><br>vs<br><br>riociguat in doses individually adjusted for each patient up to 1.5 mg three times daily<br><br>vs<br><br>placebo<br><br>All patients in riociguat group were initiated at 1 mg three times daily and dose was adjusted according to patient's systolic systemic arterial blood pressure and signs or symptoms of hypotension. | DB, MC, PC, RCT<br><br>Patients with symptomatic pulmonary arterial hypertension with pulmonary vascular resistance greater than 300 dyn·sec·cm$^{-5}$, mPAP of at least 25 mm Hg and a 6MW distance of 150 to 350 m | N=443<br><br>12 weeks | Primary:<br>Change from baseline to the end of week 12 in the 6MW distance<br><br>Secondary:<br>Changes from baseline to the end of week 12 in pulmonary vascular resistance, NT-proBNP levels, WHO functional class, clinical worsening, Borg dyspnea score, the score on the EQ-5D questionnaire and the score on the LPH questionnaire | Primary:<br>At week 12, the 6MW distance had increased from baseline by a mean of 30 m in the 2.5 mg-maximum group and had decreased by a mean of 6 m in the placebo group (least-squares mean difference, 36 m; 95% CI, 20 to 52; *P*<0.001).<br><br>Secondary:<br>Pulmonary vascular resistance decreased by 223 dyn·sec·cm$^{-5}$ in the 2.5 mg-maximum group compared to 9 dyn·sec·cm$^{-5}$ in the placebo group (least-squares mean difference, -226 dyn·sec·cm$^{-5}$; 95% CI, -281 to -170; *P*<0.001). Significant benefits were seen in the riociguat 2.5 mg-maximum group compared to the placebo group with respect to NT-proBNP levels (*P*<0.001), WHO functional class (*P*=0.003) and the Borg dyspnea score (*P*=0.002). Riociguat treated patients experienced a significant delay in time to clinical worsening compared to placebo treated patients (*P*=0.0046). The EQ-5D score did not differ significantly between the 2.5 mg-maximum group and the placebo group (*P*=0.07). There was a nominally significant difference between the 2.5 mg-maximum group and the placebo group in LPH questionnaire score (*P*=0.002).<br><br>The analysis of the 1.5 mg-maximum group was exploratory and the data from the group were not included in the efficacy analyses. |

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| Galie et al[30] (SUPER-1)<br><br>Sildenafil titrated to 80 mg three times daily as tolerated | DB, MC, PC, RCT (1:1:1:1)<br><br>Patients (mean, 47 to 51 years of age) with symptomatic PAH (either idiopathic or associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts) | N=278<br><br>12 weeks | Primary:<br>Change from baseline in 6MWD<br><br>Secondary:<br>Change in mean pulmonary artery pressure, BDI, WHO functional class, incidence of clinical worsening, and safety | Primary:<br>The 6MWD increased from baseline in all sildenafil groups with the mean placebo-corrected treatment effects of 45 (13.0%), 46 (13.3%) and 50 m (14.7%) for 20, 40 and 80 mg of sildenafil, respectively (all *P*<0.001). Among the 222 patients completing one year of treatment with sildenafil monotherapy, the improvement from baseline in the 6MWD was 51 m (95% CI, 41 to 60; *P* value not reported).<br><br>Secondary:<br>The mean pulmonary artery pressure was significantly reduced in patients receiving all sildenafil doses (*P*=0.04, *P*=0.01, and *P*<0.001 for the 20, 40 and 80 mg doses, respectively).<br><br>The change from baseline in scores on the BDI among the patients treated with sildenafil did not differ significantly from the change in patients treated with placebo.<br><br>The WHO functional class significantly improved in all sildenafil groups. After 12 weeks of treatment, the proportion of patients with an improvement of at least one functional class was 7% for placebo, and 28, 36 and 42% for sildenafil 20, 40 and 80 mg, respectively (*P*=0.003, *P*<0.001, and *P*<0.001, respectively). The incidence of clinical worsening did not differ significantly between the patients treated with sildenafil or placebo.<br><br>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. |
| Rubin et al[31] (SUPER-2)<br><br>Sildenafil 20, 40 or 80 mg three times daily<br><br>vs<br><br>placebo | ES<br><br>Patients completing SUPER-1 (mean ages 47 to 51 years) with symptomatic PAH (either | N=259<br><br>3 years | Primary:<br>Change from baseline in 6MWD, WHO functional class, survival analysis and safety<br><br>Secondary: | Primary:<br>Following three years of treatment, 122 (46%) patients increased their 6MWD relative to SUPER-1 baseline, 49 patients (18%) experienced a decrease in 6MWD from baseline, 53 (19%) patients had died and 48 (17%) patients discontinued treatment or were lost to follow-up.<br><br>The NYHA functional class status was improved (29%) or maintained (31%) in 167 patients relative to SUPER-1 baseline. Fifteen patients (5%) experienced a decline in functional status and 95 (34%) had died, discontinued or had missing |

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| If patient deterioration occurred, approved PAH therapy (including endothelin receptor antagonists and prostacyclin analogs) could be initiated. | idiopathic or associated with connective-tissue disease or with repaired congenital systemic-to-pulmonary shunts) | | Not reported | data.<br><br>The overall survival estimate at three years was 79%. Patients with idiopathic PAH had higher three-year survival rates compared to patients with PAH associated with connective tissue disease (81 vs 72%; *P* value not reported).<br><br>Patients walking ≥325 m at SUPER-1 baseline had higher three-year survival rates compared to those walking <325 m at SUPER-1 baseline (84 and 70%, respectively; *P* value not reported). For patients whose baseline walk was <325 m, deterioration in 6MWD during the first 12 weeks of sildenafil treatment was associated with lower survival (HR, 0.24; 95% CI, 0.117 to 0.498). There was no statistically significant different in the change in 6MWD and survival for those whose baseline 6MWD was ≥325 m (HR, 1.967; 95% CI, 0.687 to 5.628).<br><br>Sildenafil was generally well tolerated in the extension study, and adverse events were consistent with those that have previously been reported including headache, dyspepsia, diarrhea and blurred vision. Serious events were reported by 153 patients. Perceived treatment-related serious adverse events included grand mal seizure, drug hypersensitivity, urticaria and angioedema, gastroesophageal reflux disease, posterior subcapsular cataract and hypotension. Thirty-nine patients permanently discontinued because of adverse events. |
| Simonneau et al[32] (PACES)<br><br>Sildenafil 20 mg three times daily titrated to 40 and 80 mg three times daily, as tolerated, at four-week intervals<br><br>vs<br><br>placebo<br><br>Patients were also | DB, MC, PC, PG, RCT (1:1)<br><br>Patients (mean, 48 years of age) with PAH (idiopathic, associated anorexigen use or connective tissue disease, or corrected congenital heart disease), who | N=267<br><br>16 weeks | Primary:<br>Change from baseline in 6MWD<br><br>Secondary:<br>Change in hemodynamic parameters, BDI, time to clinical worsening, and safety | Primary:<br>The sildenafil group had a significantly greater increase in the 6MWD compared to the placebo group at week 16. The adjusted mean change at week 16 was 29.8 m for the sildenafil group and 1.0 m for the placebo group (*P*<0.001).<br><br>Secondary:<br>Compared to epoprostenol monotherapy, the addition of sildenafil resulted in a greater reduction in mean pulmonary artery pressure (-3.8 mm Hg) and cardiac output (0.9 L/minute). There was no effect on BDI with the addition of sildenafil (*P* values not reported).<br><br>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). |

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| receiving intravenous epoprostenol therapy. | were receiving long-term intravenous epoprostenol therapy (≥3 months) | | | The most commonly reported adverse events in the placebo and sildenafil groups, respectively, were headache (34 vs 57%), dyspepsia (2 vs 16%), pain in extremity (18 vs 25%) and nausea (18 vs 25%; *P* values not reported). |
| Yanagisawa et al[33]<br><br>Sildenafil 20 mg titrated up to three times daily plus epoprostenol infusion titrated to 30 ng/kg/min<br><br>vs<br><br>sildenafil 20 mg titrated up to three times daily<br><br>Patients could receive add-on bosentan or epoprostenol if sildenafil was insufficient in terms of clinical symptoms and objective findings. | MC, OL, OS<br><br>Patients with PAH (idiopathic, secondary to connective tissue disease, portal hypertension) with NYHA functional class of I to III | N=57<br><br>6 months | Primary:<br>Change from baseline in hemodynamic parameters, proportion of patient requiring epoprostenol therapy as add-on, the event-free rates according to the composite endpoint of hospitalization for right-side heart failure and death, and the estimated survival rates<br><br>Secondary:<br>Not reported | Primary:<br>Treatment with sildenafil was associated with statistically significant improvements from baseline in PVR (14.6 vs 11.6 Wood units; *P*<0.05), mean pulmonary arterial pressure (52.1 vs 45.7 mm Hg; *P*<0.01), mean right atrial pressure (8.0 vs 6.4 mm Hg; *P*<0.05) and cardiac output (3.7 vs 4.2 L/minute; *P*<0.05).<br><br>The BNP was numerically lower following sildenafil treatment; however, the difference was not statistically significant (332 vs 247 pg/mL; *P*=NS).<br><br>The 6MWD improved significantly (352 vs 422 m; *P*<0.05) with sildenafil treatment and the NYHA functional class either improved (26.1%) or maintained (65.2%) in 42 of 46 patients, and worsened in four patients (8.7%).<br><br>Hemodynamic parameters improved significantly following sildenafil monotherapy compared to baseline (mean pulmonary artery pressure, 38.0 vs 47.4 mm Hg; *P*<0.01). No statistically significant change from baseline occurred in patients receiving sildenafil plus epoprostenol (61.7 vs 61.8 mm Hg; *P*=NS).<br><br>The mean right atrial pressure was significantly reduced from baseline for patients receiving sildenafil monotherapy (5.0 vs 7.0 mm Hg; *P*<0.05), while there was no significant difference for patients receiving add-on epoprostenol (9.3 vs 10.1 mm Hg; *P*=NS).<br><br>There was a statistically significant improvement in PVR for patients treated with sildenafil alone (7.4 vs 12.8 Wood units; *P*<0.01); however, there was no significant improvement for patients receiving sildenafil plus epoprostenol (20.3 vs 18.2 Wood units; *P*=NS).<br><br>Monotherapy with sildenafil was associated with a statistically significant |

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| | | | | increase in cardiac output from baseline (*P*<0.05), while there was no significant improvement in cardiac output from baseline for patients receiving sildenafil plus epoprostenol (*P*=NS).<br><br>The percentage of patients treated without the addition of epoprostenol was 80, 70, and 63% at one, three and five years, respectively.<br><br>More than 75% of the patients had not reached the composite endpoint at five years.<br><br>Secondary:<br>Not reported |
| Galie et al[34] (PHIRST)<br><br>Tadalafil 2.5, 10, 20 or 40 mg daily<br><br>vs<br><br>placebo<br><br>Patients taking a maximal stable dose of 125 mg bosentan twice daily for a minimum of 12 weeks at the time of screening continued on bosentan in addition to study medication. | DB, DD, MC, PC, RCT<br><br>Patients (mean, 53 to 55 years of age) with symptomatic PAH (idiopathic/ heritable or related to anorexigen use, connective tissue disease, HIV infection, or congenital systemic-to-pulmonary shunts), either treatment-naïve or on background therapy with bosentan | N=405<br><br>16 weeks | Primary:<br>Change from baseline in 6MWD<br><br>Secondary:<br>Changes in WHO functional class, BDI, time to clinical worsening, changes in hemodynamic parameters, SF-36 and the EuroQol-5D questionnaire and safety | Primary:<br>Tadalafil increased the 6MWD in a dose-dependent manner. Only the 40 mg dose met the prespecified level of statistical significance (*P*<0.01) with a mean placebo-corrected treatment effect of 33 m. The treatment effect was 44 m (*P*<0.01) in bosentan-naïve patients compared to 23 m (*P*=0.09) in patients on background bosentan.<br><br>The mean change from baseline in the 6MWD for patients enrolled in the extension study was 37 m after 16 weeks of treatment and 38 m after 44 weeks of treatment (*P* values not reported).<br><br>Secondary:<br>Changes in WHO functional class and BDI were not statistically different between the tadalafil and placebo groups (*P* values not reported). Tadalafil 40 mg significantly increased the time to clinical worsening (*P*=0.041) and reduced the incidence of clinical worsening (68% RR reduction; *P*=0.038). Improvements in mean pulmonary artery pressure (*P*=0.01), PVR (*P*=0.039), and cardiac index (*P*=0.028) were reported in patients receiving tadalafil 40 mg compared to baseline.<br><br>Compared to placebo, statistically significant improvements were observed in six of the eight domains of the Study SF-36 health survey (all *P*<0.01) and for all sections of the EuroQol-5D questionnaire (all *P*<0.02) in the tadalafil 40 mg group. |

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| | | | | All doses of tadalafil were generally well tolerated, with the most common adverse events being headache, myalgia and flushing. |
| Oudiz et al[35] (PHIRST-2)<br><br>Tadalafil 20 mg daily<br><br>vs<br><br>tadalafil 40 mg daily<br><br>Changes in conventional therapies such as diuretic agents and digoxin were allowed. Patients were discontinued if they initiated prostacyclin analogs, PDE-5 inhibitors, and/or an endothelin receptor antagonist (patients receiving background bosentan at PHIRST enrollment continued on bosentan in PHIRST-2). | DB, ES, MC, PRO<br><br>Patients with symptomatic PAH who completed the PHIRST trial | N=357<br><br>52 weeks | Primary:<br>Safety, 6MWD and investigator-assessed clinical worsening<br><br>Secondary:<br>Not reported | Primary:<br>By the end of the extension phase, 92% of patients experienced at least one treatment-emergent adverse event. Forty-nine percent of events were classified by the investigator as possibly related to the study drug. Headache was the most common adverse event and occurred in 14 to 16% of patients receiving either tadalafil dose, which was lower than the 32 to 42% rate observed in the PHIRST trial.<br><br>Most adverse events were mild to moderate in intensity and did not result in study discontinuation. Thirty patients (8%) discontinued treatment due to adverse events, and 91 patients (25.5%) had serious adverse events (including 11 deaths). The majority of serious events were considered to be due to PAH-related conditions.<br><br>Kaplan-Meier survival estimates at 68 weeks for the tadalafil 20 and 40 mg doses were 95% (95% CI, 86 to 99%) and 97% (95% CI, 89 to 99%), respectively. Assuming that all discontinued patients died, survival was 66% and 75%, respectively.<br><br>For the 111 patients completing PHIRST-2, the improvements in 6MWD observed at the end of PHIRST was maintained at week 52 of PHIRST-2 (total 68 weeks).<br><br>Of patients who received tadalafil 20 or 40 mg in PHIRST, 9 and 6% experienced a worsening of WHO functional class, respectively, while 34% (for both doses) had improved WHO functional class compared to baseline of PHIRST.<br><br>The incidence of clinical worsening at 68 weeks was 27 and 22%, for patients who received tadalafil 20 or 40 mg, respectively, in PHIRST. Of patients with connective tissue disease-associated PAH, 35% had clinical worsening at week 68, compared to 24% of patients with idiopathic PAH or familial PAH and 8% of patients with other etiologies. |

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| | | | | Of patients receiving bosentan, 18% had clinical worsening at 68 weeks, compared to 31% of those not receiving bosentan. Of patients in PHIRST-2 with a baseline 6MWD ≤359 meters, 35% had clinical worsening at week 68, compared to 14% with baseline 6MWDs >359 meters.<br><br>Secondary:<br>Not reported |
| Barst et al[36]<br><br>Tadalafil 20 mg daily<br><br>vs<br><br>tadalafil 40 mg daily<br><br>vs<br><br>placebo<br><br>Patients taking a maximal stable dose of 125 mg bosentan twice daily for a minimum of 12 weeks at the time of screening continued on bosentan in addition to study medication. | DB, DD, MC, PC, RCT<br><br>Subanalysis of treatment naïve and treatment experienced patients from PHIRST | N=405<br><br>16 weeks | Primary:<br>Change from baseline in 6MWD<br><br>Secondary:<br>Changes in WHO functional class and BDI, time to clinical worsening, changes in hemodynamic parameters and safety | Primary:<br>There was no statistically significant increase in 6MWD from baseline in the 20 mg tadalafil (22.6 m; 95% CI, -0.5 to 45.7) or 40 mg tadalafil (22.7 m; 95% CI, -2.4 to 47.8) groups for patients receiving background bosentan therapy.<br><br>In treatment naïve patients, statistically significant improvements in the 6MWD were achieved in the 40 mg tadalafil (44.3 m; 95% CI, 19.7 to 69.0) and 20 mg tadalafil groups (32.4 m, 95% CI, 6.8 to 58.1).<br><br>Secondary:<br>The change in WHO functional class for the 40 mg tadalafil treatment-naive and bosentan-experienced patients suggested there was greater numeric improvement in functional class in both groups compared to placebo; however, the difference was not statistically significant (HR, 1.1; 95% CI, 0.6 to 2.2 and HR, 2.7; 95% CI, 0.8 to 8.6, respectively).<br><br>More treatment-naïve patients were considered to clinically worsen over the treatment period compared to patients with background bosentan therapy. Treatment with placebo was associated with greater risk of clinical worsening compared to tadalafil 40 mg in treatment-naïve patients (HR, 3.3; 95% CI, 1.1 to 10.0). There was no difference in clinical worsening compared to placebo for patients receiving tadalafil 40 mg who were also receiving concomitant bosentan (HR, 1.9; 95% CI, 0.4 to 10.2).<br><br>Changes from baseline in PVR were similar for the tadalafil 20 and 40 mg treatment groups, regardless of bosentan treatment.<br><br>Similar treatment-related adverse events and overall incidence were observed in |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | both groups. Headache was the most common adverse event in the tadalafil groups. Dizziness and dyspepsia were also frequently reported among the treatment groups. Across all tadalafil treatment subgroups, approximately twice as many discontinuations occurred in the treatment-naive group as in the background bosentan group (31 vs 18), the majority due to disease progression. |
| McLaughlin et al[37] (TRIUMPH-1)<br><br>Treprostinil 18 µg inhaled four times daily, titrated up over the first two weeks to 54 µg four times daily if tolerated<br><br>vs<br><br>placebo<br><br>Patients were also receiving either bosentan or sildenafil therapy. | DB, MC, PC, RCT<br><br>Patients 18 to 75 years of age with idiopathic or familiar PAH or PAH associated with collagen vascular disease, HIV infection, or anorexigen use (NYHA class III or IV symptoms), receiving bosentan or sildenafil for ≥3 months prior to study | N=235<br><br>12 weeks | Primary:<br>Change in 6MWD measured at peak (10 to 60 minutes after inhalation)<br><br>Secondary:<br>Time to clinical worsening, BDI, NYHA functional class, PAH signs and symptoms, trough 6MWD (at least four hours after drug administration), peak 6MWD at six weeks, and quality of life as measured by the MLWHF questionnaire | Primary:<br>After 12 weeks, the change from baseline in peak 6MWD between treatments was 20 m, favoring treprostinil (*P*=0.0004). Between-treatment median difference in change in peak 6MWD was 25 m (*P*=0.0002) in patients receiving background bosentan therapy and 9 m in patients taking sildenafil background therapy (*P*=NS).<br><br>Secondary:<br>There was no difference in time to clinical worsening, change in BDI, NYHA functional classification, or PAH signs and symptoms between the treprostinil and placebo treatment groups.<br><br>At six weeks, the between-treatment difference in peak 6MWD was 19 m (*P*=0.0001) favoring the treprostinil group over placebo. At week 12, the change in trough 6MWD was 14 m (*P*=0.0066) favoring the treprostinil group over placebo.<br><br>Patients receiving inhaled treprostinil had significant improvements in their quality of life as assessed by the MLWHF questionnaire, in the global score (*P*=0.027) and in the physical score (*P*=0.037). |
| Benza et al[38]<br><br>Treprostinil 18 µg inhaled four times daily, titrated up over the first two weeks to 54 µg four times daily if tolerated | ES, OL<br><br>Patients 18 to 75 years of age with idiopathic or familiar PAH or PAH associated with collagen | N=206<br><br>24 months | Primary:<br>Peak 6MWD, BDI, NYHA functional class, evaluation of PAH signs and symptoms, quality of life | Primary:<br>The median changes in 6MWD after six, 12, 18 and 24 months of treprostinil treatment were 28, 31, 32 and 18 m (*P*≤0.013 for all), respectively. The percentage of patients receiving treprostinil who were able to walk >440 m increased from 13% at baseline to 26% at 24 months (*P* value not reported).<br><br>At the completion of each 6MWD, the BDI improved from baseline; however, the difference was only significant at month six (-0.37; *P*<0.02). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>placebo<br><br>Patients were also receiving either bosentan or sildenafil therapy. | vascular disease, HIV infection, or anorexigen use (NYHA class III or IV symptoms), receiving bosentan or sildenafil for ≥3 months prior to study who completed the TRIUMPH trial | | questionnaire and adverse events<br><br>Secondary:<br>Not reported | With regard to NYHA class, >90% of participants had improvement or no change from baseline. Specifically, the number of patients who improved from baseline in NYHA class was 36, 37, 34 and 36% at six, 12, 18 and 24 months, respectively (*P* value not reported).<br><br>There were significant improvements in all quality of life dimensions (physical, global and emotional) through 24 months of treprostinil treatment (*P* value not reported).<br><br>The overall survival for patients who remained in the study was 97, 94 and 91% at 12, 18 and 24 months, respectively. Clinical worsening (defined as, time to first event; addition of a new PAH therapy, discontinuation due to disease progression or death) was evaluated at 12, 18 and 24 months, and 82, 74 and 69% of patients, respectively, did not experience an event while on therapy (*P* value not reported).<br><br>The most common adverse events were cough (53%), headache (34%) and nausea (21%). Adverse events leading to discontinuation from the study occurred in 40 patients (19%), which included worsening PAH (5%), cough (4%) and headache (2%). Of 14 deaths that occurred during the open-label extension, none were considered attributable to inhaled treprostinil. |
| Perez et al[39]<br><br>Treprostinil 18 µg inhaled four times daily, titrated up over the first two weeks to 54 µg four times daily if tolerated | MC, RETRO<br><br>Patients with WHO group I PAH who were initially started on intravenous/ subcutaneous treprostinil or intravenous epoprostenol and later switched to inhaled treprostinil | N=18<br><br>7 months | Primary:<br>Change in 6MWD, BNP, NYHA functional class, adverse events<br><br>Secondary:<br>Not reported | Primary:<br>There was no statistically significant change from baseline in 6MWD for patients transitioned from epoprostenol to treprostinil over seven months (427 vs 447 m; *P*>0.05).<br><br>Similarly, no change from baseline in BNP was observed for patients transitioning from epoprostenol to treprostinil therapy (151 vs 168 pg/mL; *P*>0.05).<br><br>There was a significant worsening of NYHA functional class (22 vs 33%; *P*=0.006) and BNP (354 vs 496 pg/mL; *P*<0.05) following transition to treprostinil.<br><br>After transition, there were no reports of diarrhea (compared to nine at baseline |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | with epoprostenol) and most patients reported improvement in myalgia (seven patients at baseline and one patient following the initiation of treprostinil). There were new symptoms of cough and syncope (three patients each) following the initiation of treprostinil therapy.<br><br>Secondary:<br>Not reported |
| Benza et al[40]<br><br>Treprostinil subcutaneous infusion titrated based on symptoms, exercise capacity and adverse events<br><br>vs<br><br>treprostinil subcutaneous infusion titrated based on symptoms, exercise capacity and adverse events plus bosentan 62.5 mg twice daily titrated to 125 mg twice daily<br><br>The addition of bosentan to therapy was considered if patients were persistently in NYHA functional class III or worse, or were in NYHA class II and were experiencing adverse | OL, RETRO<br><br>Patients with PAH diagnosed by WHO criteria | N=38<br><br>24 months | Primary:<br>Change in 6MWD, hemodynamic parameters and safety<br><br>Secondary:<br>Not reported | Primary:<br>Patients receiving long-term treprostinil-based therapy experienced statistically significant increase in their 6MW distance from 306 m at baseline to 341 m at the last follow-up (*P*=0.022). No statistically significant difference was reported when bosentan was added to therapy compared to treprostinil alone (307.2 vs 304.6 m; *P*>0.05).<br><br>The BDI was significantly improved, from 3.8 to 2.9, respectively (*P*=0.023). Treprostinil treatment also significantly improved NYHA functional class compared to baseline (*P*<0.0001). There was no statistically significant difference in NYHA functional classes between treprostinil monotherapy and the addition of bosentan.<br><br>Patients receiving long-term treprostinil-based therapy demonstrated favorable effects on hemodynamics and exercise tolerance at the last follow-up. The mean pulmonary artery pressure decreased from 59.7 to 50.5 mm Hg at the end of treatment (*P*<0.001). The addition of bosentan did not significantly improve pulmonary artery pressures compared to treprostinil alone (59.7 vs 59.6; *P*>0.05).<br><br>The mean cardiac output increased from 4.92 to 5.34 L/minute with treprostinil therapy (*P*=0.028). The addition of bosentan did not significantly improve cardiac output compared to treatment with treprostinil alone (5.15 vs 4.66; *P*>0.05).<br><br>There was no statistically significant improvement from baseline in PVR (814.1 vs 705.2 dynes/sec/cm$^{-5}$ (*P*=0.113). Combination therapy was associated with a lower PVR compared to treprostinil monotherapy; however, the difference was not statistically significant (764.6 vs 867.2 dynes/sec/cm$^{-5}$; *P*>0.05). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| events from prostacyclin-based therapy, necessitating a dose reduction. | | | | Small, but statistically significant, changes from baseline to final laboratory measurements were observed for AST, ALT and hemoglobin values with combination therapy ($P$<0.05 for all).<br><br>Secondary:<br>Not reported |

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, ED=event driven, ES=extension study, HR=hazard ratio, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, RETRO=retrospective study, RR=relative risk
Miscellaneous abbreviations: 6MWD=6-minute walk distance, ALT=alanine aminotransferase, AST=aspartate aminotransferase, BDI=Borg Dyspnea Index, BNP= brain natriuretic peptide, CI=confidence interval, EuroQol=European quality of life questionnaire, EQ-5D=EuroQol Group 5-Dimension Self-Report, $FEV_1$=forced expiratory volume in 1 second, HIV=human immunodeficiency virus, HRQoL=health-related quality of life, LPH=Living with Pulmonary Hypertension, MCS=mental component score, MLWHF=Minnesota Living with Heart Failure, mm Hg=millimeters in mercury, NT-proBNP=N-terminal pro-brain natriuretic peptide, NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, PCS=physical component score, PVR=pulmonary vascular resistance, SF-36=short form-36 health survey, VAS=visual analog scale, WHO=World Health Organization, WHO-FC=World Health Organization functional classification

## Special Populations

**Table 5. Special Populations[1-8]**

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Ambrisentan | No dosage adjustment required in elderly patients.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment in mild to moderate renal impairment required. | Not studied in hepatic dysfunction.<br><br>Not recommended in patients with moderate or severe hepatic impairment. | X | Unknown; breastfeeding not recommended. |
| Bosentan | Not studied in the elderly.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required. | Not studied in moderate or severe hepatic dysfunction.<br><br>Not recommended in patients with moderate or severe hepatic impairment. | X | Unknown |
| Iloprost | Not studied in the elderly.<br><br>Safety and efficacy in children have not been established. | Not studied in renal dysfunction. | Not studied in hepatic dysfunction. | C | Unknown |
| Macitentan | No dosage adjustment required in the elderly.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required. | No dosage adjustment required. | X | Unknown; breastfeeding not recommended. |
| Riociguat | No dosage adjustment required in the elderly.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment in mild to moderate renal impairment required.<br><br>Safety and efficacy have not been demonstrated in patients with | Not studied in mild or moderate hepatic dysfunction.<br><br>Not recommended in patients with severe hepatic dysfunction. | X | Unknown; breastfeeding not recommended. |

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| | | creatinine clearance <15 mL/min or on dialysis. | | | |
| Sildenafil | Not studied in the elderly.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required. | No dosage adjustment required in mild to moderate dysfunction.<br><br>Not studied in severe dysfunction. | B | Unknown |
| Tadalafil | No dosage adjustment required in the elderly.<br><br>Safety and efficacy in children have not been established. | Dosage adjustment is required for patients with mild-to-moderate dysfunction.<br><br>Use is not recommended in patients with severe dysfunction. | Dosage adjustment is required for patients with mild-to-moderate dysfunction.<br><br>Use is not recommended in patients with severe dysfunction. | B | Unknown |
| Treprostinil inhalation solution | Not studied in the elderly.<br><br>Safety and efficacy in children have not been established. | Not studied in renal dysfunction. | Dosage adjustment is required for patients with mild-to-moderate dysfunction.<br><br>Not studied in severe dysfunction. | B | Unknown |

**Adverse Drug Events**

Common adverse events in the class of prostanoids are jaw pain, diarrhea, headache and flushing. Endothelin receptor antagonists are associated with peripheral edema and elevated liver function tests. The phosphodiesterase-5 inhibitors are generally well tolerated and common adverse effects are headache, flushing and dyspepsia. The most common adverse events associated with the soluble guanylate cyclase stimulators can be ascribed to the vasodilatory mechanism of action, including headache, dizziness, nausea and hypotension.

**Table 6. Adverse Drug Events (%)[1-8,12]**

| Adverse Event(s) | Ambrisentan | Bosentan | Iloprost | Macitentan | Riociguat | Sildenafil | Tadalafil | Treprostinil Inhalation Solution |
|---|---|---|---|---|---|---|---|---|
| Abdominal distension | - | - | - | - | ✔ | - | - | - |
| Anemia | 7 to 10 | 3 to 6 | - | 13 | 7 | - | - | - |
| Asthenia | ✔ | - | - | - | - | - | - | - |
| Arthralgia | - | 4 | - | - | - | - | - | - |
| Back pain | - | - | 7 | - | - | - | 10 to 12 | - |
| Bronchitis | - | - | - | 12 | - | - | - | - |
| Chest pain | - | 5 | - | - | - | - | - | - |
| Constipation | - | - | - | - | 5 | - | - | - |
| Cough increased | - | - | 39 | - | - | - | - | 54 |
| Diarrhea | - | - | - | - | 12 | 9 | - | - |
| Dizziness | ✔ | - | - | - | 20 | - | - | - |
| Dyspepsia | - | - | - | - | 21 | 13 | 10 to 13 | - |
| Dysphagia | - | - | - | - | ✔ | - | - | - |
| Dyspnea, exacerbated | - | - | - | - | - | 7 | - | - |
| Edema | - | 11 | - | - | - | - | - | - |
| Elevated alanine aminotransferase | ✔ | 11 to 14 | - | ✔ | - | - | - | - |
| Elevated aspartate aminotransferase | ✔ | - | - | ✔ | - | - | - | - |
| Epistaxis | - | - | - | - | ✔ | 9 | - | - |
| Erythema | - | - | - | - | - | 6 | - | - |
| Fatigue | ✔ | - | - | - | - | - | - | - |
| Flu-like syndrome | - | - | 14 | - | - | - | - | - |
| Fluid retention | ✔ | - | - | - | - | - | - | - |
| Flushing | 4 | 4 | 27 | - | - | 10 | 6 to 13 | 15 |
| Gastritis | - | - | - | - | 21 | 3 | - | - |
| Gastroesophageal reflux | - | - | - | - | 5 | - | - | - |
| Headache | 15 | 15 | 30 | 14 | 27 | 46 | 32 to 42 | 41 |

| Adverse Event(s) | Ambrisentan | Bosentan | Iloprost | Macitentan | Riociguat | Sildenafil | Tadalafil | Treprostinil Inhalation Solution |
|---|---|---|---|---|---|---|---|---|
| Hearing impairment | - | - | - | - | - | ✔ | ✔ | - |
| Heart failure | ✔ | - | - | - | - | - | - | - |
| Hemoptysis | - | - | 5 | - | - | - | - | - |
| Hypersensitivity | ✔ | - | - | - | - | - | - | - |
| Hypotension | - | 4 | 11 | - | 10 | ✔ | ✔ | - |
| Influenza | - | - | - | 6 | - | - | - | - |
| Insomnia | - | - | 8 | - | - | 7 | - | - |
| Myalgia | - | - | - | - | - | 7 | 9 to 14 | - |
| Muscle cramps | - | - | 6 | - | - | - | - | - |
| Nasal congestion | 6 | - | - | - | ✔ | - | 9 | - |
| Nasopharyngitis | - | - | - | 20 | - | - | 2 to 13 | - |
| Nausea | ✔ | - | 13 | - | 14 | - | 10 to 11 | 19 |
| Palpitations | - | 4 | 7 | - | ✔ | - | - | - |
| Pain in extremity | - | - | - | - | - | - | 5 to 11 | - |
| Paresthesia | - | - | - | - | - | 3 | - | - |
| Peripheral edema | 17 | 11 | - | - | ✔ | - | - | - |
| Pneumonia | - | 4 | - | - | - | - | - | - |
| Priapism | - | - | - | - | - | - | ✔ | - |
| Pyrexia | - | - | - | - | - | 6 | - | - |
| Respiratory tract infection | - | 22 | - | - | - | - | 7 to 13 | - |
| Rhinitis | - | - | - | - | - | 4 | - | - |
| Serum aminotransferases abnormal | - | 4 | - | - | - | - | - | - |
| Sinusitis | 3 | 4 | - | - | - | 3 | - | - |
| Syncope | - | 5 | 8 | - | - | - | - | 6 |
| Trismus | - | - | 12 | - | - | - | - | - |
| Throat irritation/ nasopharyngeal pain | - | - | - | - | - | - | - | 25 |
| Tongue pain | - | - | 4 | - | - | - | - | - |
| Urinary tract infection | - | - | - | 9 | - | - | - | - |
| Vision Loss | - | - | - | - | - | ✔ | ✔ | - |
| Vomiting | ✔ | - | 7 | - | 10 | - | - | - |

✔ Percent not specified.
- Event not reported or incidence <1%.

## Contraindications

**Table 7. Contraindications[1-6,10]**

| Contraindication | Ambrisentan | Bosentan | Iloprost | Macitentan | Riociguat | Sildenafil | Tadalafil | Treprostinil Inhalation Solution |
|---|---|---|---|---|---|---|---|---|
| Concomitant use with cyclosporine A or glyburide | - | ✔ | - | - | - | - | - | - |
| Concomitant use with phosphodiesterase inhibitors | - | - | - | - | ✔ | - | - | - |
| Hypersensitivity to any component of the product | - | ✔ | - | - | - | ✔ | ✔ | - |
| Idiopathic pulmonary fibrosis | ✔ | - | - | - | - | - | - | - |
| Regular or intermittent use of organic nitrates | - | - | - | - | ✔ | ✔ | ✔ | - |
| Women who are or may become pregnant | ✔ | ✔ | - | ✔ | ✔ | - | - | - |

**Black Box Warning for Ambrisentan[2]**

| WARNING |
| --- |
| Warning: Contraindicated in Pregnancy<br>Do not administer ambrisentan to a pregnant woman because it may cause fetal harm. 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.<br><br>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.<br><br>Because of the risk of birth defects, ambrisentan is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Letairis® Education and Access Program (LEAP). As a component of the ambrisentan prescribers, patients, and pharmacies must enroll in the program. |

**Black Box Warning for Bosentan[3]**

| WARNING |
| --- |
| Because of the risk of liver injury and birth defects, bosentan is available only through a special restricted distribution program called the Tracleer Access Program (T.A.P.), by calling 1-866-228-3546. Only prescribers and pharmacies registered with T.A.P. may prescribe and distribute bosentan. In addition, bosentan may be dispensed only to patients who are enrolled in and meet all conditions of T.A.P.<br><br>Liver Injury<br>In clinical studies, bosentan caused at least three-fold upper limit of normal elevation of liver aminotransferases (aspartate aminotransferase and alanine aminotransferase) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious liver injury, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (>12 months) therapy with bosentan in patients with multiple co-morbidities and drug therapies. There have also been reports of liver failure. The contribution of bosentan in these cases could not be excluded.<br><br>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.<br><br>Elevations in aminotransferases require close attention. Bosentan should generally be avoided in patients with elevated aminotransferases (>3 times upper limit of normal) 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 times upper limit of normal, treatment with bosentan should be stopped. There is no experience with the re-introduction of bosentan in these circumstances.<br><br>Teratogenicity<br>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 |

| WARNING |
| --- |
| 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. |

**Black Box Warning for Macitentan[7]**

| WARNING |
| --- |
| • Do not administer Opsumit® (macitentan) to a pregnant female because it may cause fetal harm.<br>• Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment and one month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.<br>• For all female patients, Opsumit® (macitentan) is available only through a restricted program called the Opsumit® (macitentan) Risk Evaluation and Mitigation Strategy (REMS) |

**Black Box Warning for Riociguat[8]**

| WARNING |
| --- |
| Warning: Contraindicated in Pregnancy<br>Do not administer riociguat to a pregnant woman because it may cause fetal harm.<br><br>Pregnancy must therefore be excluded before the initiation of treatment with riociguat and prevented during treatment and for one month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception.<br><br>Because of the risk of birth defects, riociguat is available only through a restricted program called the Adempas® Risk Evaluation and Mitigation Strategy (REMS) Program. |

## Warnings/Precautions

**Table 8. Warnings and Precautions[1-8,12]**

| Warning/Precaution | Ambri-sentan | Bos-entan | Iloprost | Maci-tentan | Rio-ciguat | Sild-enafil | Tad-alafil | Treprostinil Inhalation Solution |
|---|---|---|---|---|---|---|---|---|
| Availability restricted through specialty distribution program | ✔ | ✔ | - | ✔ | ✔ | - | - | - |
| Bleeding risk may be increased, particularly in patients receiving anticoagulants | - | - | - | - | ✔ | - | - | ✔ |
| Combination use with other phosphodiesterase-5 inhibitors has not been evaluated | - | - | - | - | - | ✔ | ✔ | - |
| Consider pulmonary veno-occlusive disease if acute pulmonary edema develops | ✔ | ✔ | - | ✔ | ✔ | - | - | - |
| Decreased sperm counts have been reported with endothelin receptor antagonists | ✔ | ✔ | - | ✔ | - | - | - | - |
| Decreased hemoglobin and hematocrit concentrations may develop following initiation of treatment | ✔ | ✔ | - | ✔ | - | - | - | - |
| Effectiveness in pulmonary hypertension secondary to sickle cell disease has not been established | - | - | - | - | - | ✔ | - | - |
| Elevations of aspartate aminotransferase and/or alanine transaminase are typically asymptomatic, and usually have been reversible after treatment interruption or cessation | - | ✔ | - | - | - | - | - | - |
| Hearing loss, tinnitus and dizziness have been reported with use | - | - | - | - | - | ✔ | ✔ | - |
| If clinical symptoms of liver injury (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2x the upper limit of normal occur, treatment should be discontinued | - | ✔ | - | ✔ | - | - | - | - |
| Liver aminotransferase levels must be measured prior to initiation of treatment and then monthly | - | ✔ | - | - | - | - | - | - |
| May cause fetal harm when administered during pregnancy and is contraindicated for use in females who are pregnant. | ✔ | - | - | - | ✔ | - | - | - |
| May induce bronchospasm and may be more | - | - | ✔ | - | - | - | - | - |

| Warning/Precaution | Ambri-sentan | Bos-entan | Iloprost | Maci-tentan | Rio-ciguat | Sild-enafil | Tad-alafil | Treprostinil Inhalation Solution |
|---|---|---|---|---|---|---|---|---|
| severe in patients with a history of hyperreactive airways | | | | | | | | |
| May worsen cardiovascular status of patients with pulmonary veno-occlusive disease | - | - | - | - | - | ✔ | ✔ | - |
| Medication should not come in contact with the eyes or skin | - | - | ✔ | - | - | - | - | - |
| Mild and transient decrease in blood pressure may occur due to vasodilator properties | - | - | - | - | - | ✔ | ✔ | - |
| Moderate to severe hepatic impairment | - | ✔ | - | - | - | - | - | - |
| Mortality with pediatric use; results from long-term trials indicated increased mortality in pediatric patients | - | - | - | - | - | ✔ | - | - |
| Peripheral edema has been reported postmarketing surveillance | ✔ | ✔ | - | - | - | - | - | - |
| Priapism; patients experiencing an erection lasting longer than four hours should seek medical attention | - | - | - | - | - | ✔ | ✔ | - |
| Pulmonary edema has been reported with treatment | - | - | ✔ | - | - | - | - | - |
| Safety and efficacy have not been established in patients with significant underlying lung disease (e.g., asthma or chronic obstructive pulmonary disease) or pulmonary infections | - | - | - | - | - | - | - | ✔ |
| Safety and efficacy in patients with a history of mitral valve disease, pericardial constriction, congestive cardiomyopathy, left ventricular dysfunction, life-threatening arrhythmias, coronary artery disease and uncontrolled hypertension is unknown | - | - | - | - | - | - | ✔ | - |
| Safety and efficacy in patients with a history of myocardial infarction, life-threatening arrhythmia in previous six months, coronary artery disease, hypertension or concurrent bosentan therapy is unknown | - | - | - | - | - | ✔ | - | - |
| Safety in patients with bleeding disorders or active peptic ulceration is unknown | - | - | - | - | - | ✔ | ✔ | - |
| Seek immediate medical attention in the event of | - | - | - | - | - | ✔ | ✔ | - |

| Warning/Precaution | Ambri-sentan | Bos-entan | Iloprost | Maci-tentan | Rio-ciguat | Sild-enafil | Tad-alafil | Treprostinil Inhalation Solution |
|---|---|---|---|---|---|---|---|---|
| sudden vision loss in one or both eyes | | | | | | | | |
| Symptomatic hypotension may occur in patients with hypovolemia, severe left ventricular outflow obstruction, resting hypotension or autonomic dysfunction. | - | - | - | - | ✔ | - | - | - |
| Symptomatic hypotension may occur in patients with low systemic arterial pressures | - | - | - | - | - | - | - | ✔ |
| Syncope has been reported; do not initiate treatment in patients with a systolic blood pressure of less than 85 mm Hg | - | - | ✔ | - | - | - | - | - |

## Drug Interactions

**Table 9. Drug Interactions[1-8,12]**

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Bosentan, sildenafil, tadalafil | Ritonavir | Ritonavir may increase bosentan concentration. Coadministration of ritonavir and sildenafil is not recommended. The dosage of tadalafil may require adjustment in patients receiving ritonavir. |
| Iloprost, tadalafil, treprostinil | Diuretics, antihypertensives, vasodilators | Concomitant administration may potentiate hypotensive effects. |
| Riociguat, sildenafil, tadalafil | Alpha-blockers | Caution is advised when riociguat, sildenafil and tadalafil are coadministered with alpha-blockers since both are vasodilators with blood pressure lowering effects. |
| Riociguat, sildenafil, tadalafil | Nitrates (and nitric oxide donors) | Administration of sildenafil and tadalafil with nitrates in any form (regularly and/or intermittently) is contraindicated. Sildenafil and tadalafil may potentiate the hypotensive effects of nitrates. When nitrate administration is deemed medically necessary for a life-threatening situation, at least 48 hours should have elapsed after the last dose of tadalafil before nitrate administration is considered. In such circumstances, nitrates should still only be administered under close medical supervision with appropriate hemodynamic monitoring. A suitable time interval following sildenafil dosing for the safe administration of nitrates or nitric oxide donors has not been determined. |
| Ambrisentan, bosentan | Cyclosporine | Cyclosporine may increase ambrisentan exposure; limit the dose to 5 mg daily. Coadministration of bosentan and cyclosporine is contraindicated because it may lead to decreased cyclosporine and increased bosentan plasma concentrations. |
| Iloprost, treprostinil | Antiplatelet agents and anticoagulants | Because iloprost and treprostinil inhibit platelet aggregation, there may be an increased risk of bleeding. |
| 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. |
| Riociguat | Phospho-diesterase inhibitors | Concomitant administration may potentiate hypotensive effects. |
| Riociguat | Strong CYP and P-gp/BCRP inhibitors | Concomitant administration may increase riociguat exposure and may result in hypotension. Consider a starting dose of 0.5 mg three times daily when initiating riociguat in patients taking a strong CYP and P-gp/BCRP inhibitor. |
| Riociguat | Strong CYP3A inducers | Concomitant administration may significantly reduce riociguat exposure. Data are not available to guide dosing of riociguat when strong CYP3A inducers are coadministered. |
| Macitentan | Strong CYP3A4 inducers | Strong inducers of CYP3A4 may significantly reduce macitentan exposure by increasing its metabolism. Concomitant use of macitentan with strong CYP3A4 inducers should be avoided. |
| Macitentan | Strong CYP3A4 inhibitors | Strong inhibitors of CYP3A4 may increase the exposure of macitentan by decreasing its metabolism. Concomitant use of macitentan with strong CYP3A4 inhibitors should be avoided. |

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| Bosentan | Glyburide | Coadministration of bosentan and glyburide is contraindicated it may lead to increased risk of elevated liver enzymes. |
| Tadalafil | Rifampin | Rifampin may decrease tadalafil plasma concentration. Avoid use of tadalafil in patients receiving rifampin. |
| Treprostinil | Antiplatelet agents and anticoagulants | Because epoprostenol, iloprost, and treprostinil inhibit platelet aggregation, there may be an increased risk of bleeding. |
| Treprostinil | Diuretics, antihypertensives, vasodilators | Concomitant administration may potentiate hypotensive effects. |

BCRP=breast cancer resistance protein, P-gp=P-glycoprotein

**Dosage and Administration**

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

**Table 10. Dosing and Administration[1-8,12]**

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Ambrisentan | Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening:<br>Tablet: initial, 5 mg QD; may increase up to 10 mg QD if 5 mg is tolerated | Safety and efficacy in children have not been established. | Tablet:<br>5 mg<br>10 mg |
| Bosentan | Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening:<br>Tablet: initial, 62.5 mg BID for four weeks; maintenance, 125 mg BID | Safety and efficacy in children have not been established. | Tablet:<br>62.5 mg<br>125 mg |
| Iloprost | Treatment of PAH (WHO Group I) to improve a composite endpoint consisting of exercise tolerance symptoms (NYHA class) and lack of deterioration:<br>Ampule for inhalation: initial dose, 2.5 µg/dose; maintenance, 5 µg/dose if tolerated (otherwise, 2.5 µg/dose); administer six to nine times daily (no more frequently than every two hours) while awake; maximum, 45 µg daily | Safety and efficacy in children have not been established. | Ampule for inhalation:<br>10 µg/mL<br>20 µg/mL<br><br>This mediation is available only through specialty pharmacies. |
| Macitentan | Treatment of PAH (WHO Group I) to delay disease progression:<br>Tablet: 10 mg daily | Safety and efficacy in children have not been established. | Tablet:<br>10 mg |
| Riociguat | Treatment of CTEPH and PAH (WHO Group I) to improve exercise ability, WHO functional class and delay clinical worsening:<br>Tablet: initial, 1 mg TID; increase dosage by 0.5 mg at intervals of at least two weeks as tolerated; if hypotensive effects are not tolerated, an initial dose of 0.5 mg TID may be required; maximum dose, 2.5 mg TID | Safety and efficacy in children have not been established. | Tablet:<br>0.5 mg<br>1 mg<br>1.5 mg<br>2 mg<br>2.5 mg |
| Sildenafil | Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening:<br>Tablet: 20 mg TID, approximately four to six hours apart; doses above 20 mg TID are not | Safety and efficacy in children have not been established. | Tablet:<br>20 mg<br><br>Vial for |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | recommended<br><br>Vial for intravenous injection: 10 mg TID | | injection: 0.8 mg/mL |
| Tadalafil | Treatment of PAH (WHO Group I) to improve exercise ability:<br>Tablet: 40 mg QD; dividing the dose over the course of the day is not recommended | Safety and efficacy in children have not been established. | Tablet: 20 mg |
| Treprostinil inhalation solution | Treatment of PAH (WHO Group I) to improve exercise ability:<br>Ampule for inhalation: initial, 18 µg (three inhalations) QID while awake; if three inhalations are not tolerated, reduce to one or two inhalations, then increase to three inhalations as tolerated; maintenance, if tolerated, increase dose by an additional three inhalations at approximately one to two week intervals; maximum dose, 54 µg (nine inhalations) QID | Safety and efficacy in children have not been established. | Ampule for inhalation: 0.6 mg/mL<br><br>This mediation is available only through specialty pharmacies. |

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

## Clinical Guidelines

**Table 11. Clinical Guidelines**

| Clinical Guideline | Recommendations |
|---|---|
| American College of Cardiology Foundation/ American Heart Association: **Expert Consensus Document on Pulmonary Hypertension* (2009)**[10] | • Goals of treatment include improvement in the patient's symptoms, quality of life, and survival.<br>• 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.<br>• Background therapies may include warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Oral calcium-channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing. The most commonly used CCBs include long-acting nifedipine, diltiazem, and amlodipine, while verapamil should be avoided due to its potential negative inotropic effects.<br>• For patients who do not have a positive acute vasodilator response to testing and are considered lower risk based on clinical assessment, oral therapy with endothelin receptor antagonists (ERAs) or phosphodiesterase (PDE)-5 inhibitors are the recommended first-line therapy. If an oral regimen is not appropriate, other treatments would need to be considered based on the patient's profile adverse events and risk of each therapy. In general, patients with poor prognostic indexes should be initiated on intravenous epoprostenol or treprostinil therapy, while patients with class II or early III symptoms commonly commence therapy with either ERAs or PDE-5 inhibitors.<br>• For patients who are considered high risk based on clinical assessment, continuous treatment with an intravenous prostacyclin (epoprostenol or treprostinil) would be the first-line of therapy recommended. If a patient is not a candidate for continuous intravenous treatment, other therapies would have to be considered based on the patient's profile, adverse events 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. |

| Clinical Guideline | Recommendations |
|---|---|
| | Although expensive and difficult to administer, epoprostenol is the only therapy for PAH that has been shown to prolong survival. Treprostinil may be delivered via either continuous intravenous or subcutaneous infusion. Iloprost is a prostacyclin analogue delivered by an adaptive aerosolized device six times daily. The ERAs are oral therapies that improve exercise capacity in PAH. Liver function tests must be monitored indefinitely on a monthly basis. The PDE-5 inhibitors also improve exercise capacity and hemodynamics in PAH.<br>• Combination therapy should be considered when patients are not responding adequately to initial monotherapy.<br><br>(Note: at the time when this document was published, tadalafil and treprostinil inhalation solution were not Food and Drug Administration (FDA)-approved for the treatment of PAH. In March 2011, the prescribing information for ambrisentan was updated to no longer require monthly monitoring of liver function tests.) |
| American College of Chest Physicians: **Medical Therapy for Pulmonary Arterial Hypertension (2007)**[13] | • Warfarin and supplemental oxygen are recommended in selected patient populations.<br>• In the absence of right-heart failure, patients with idiopathic PAH or PAH associated with underlying processes such as scleroderma or congenital heart disease, who demonstrate a favorable acute response to a vasodilator, should be considered candidates for a trial of therapy with an oral CCB. CCBs should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity.<br>• PAH patients in functional class II who are not candidates for, or who have failed, CCB therapy, may benefit from treatment with sildenafil or subcutaneous or intravenous treprostinil. Although treprostinil is FDA-approved for use in patients in functional class II, it would seldom be recommended due to the complexity of administration, adverse events, and cost.<br>• PAH patients in functional class III who are not candidates for, or who have failed, CCB therapy, are candidates for long-term therapy with ERAs or sildenafil, in no order of preference. Alternatives include intravenous epoprostenol, inhaled iloprost or treprostinil.<br>• PAH patients in functional class IV who are not candidates for, or who have failed, CCB therapy are candidates for long-term therapy with intravenous epoprostenol (treatment of choice). Other treatments available, in no order of preference, include ERAs, inhaled iloprost, subcutaneous or intravenous treprostinil and sildenafil.<br><br>(Note: at the time when this document was published, ambrisentan, tadalafil and treprostinil inhalation solution were not FDA-approved for the treatment of PAH.) |
| European Society of Cardiology/ European Respiratory Society: **Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension**† **(2009)**[14] | • Selected patients with PAH may be candidates for supportive therapy with oral anticoagulants, diuretics, oxygen and digoxin.<br>• Patients with idiopathic PAH and positive vasodilator response should be treated with a CCB. The CCBs commonly used in studies are nifedipine, diltiazem, and amlodipine, with particular emphasis on the first two. Nifedipine and amlodipine are recommended in patients with a relative bradycardia, while diltiazem is appropriate for patients with a relative tachycardia.<br>• Patients who have not undergone a vasoreactivity study or those with a negative study should not be started on a CCB because of potential for severe adverse events (e.g., hypotension, syncope and right ventricular |

| Clinical Guideline | Recommendations |
|---|---|
| | failure).<br>• Non-responders to acute vasoreactivity testing who are in World Health Organization (WHO)-functional class II should be treated with an ERA or a PDE-5 inhibitor.<br>• Non-responders to acute vasoreactivity testing, or responders who remain in (or progress to) WHO-functional class III should be considered candidates for treatment with either an ERA or a PDE-5 inhibitor, or a prostanoid.<br>• As head-to-head comparisons among different compounds are not available, no evidence-based first-line treatment can be proposed. The choice of the drug is dependent on a variety of factors including the approval status, the route of administration, the adverse event profile, patients' preferences, and physicians' experience. Some experts still use first-line intravenous epoprostenol in WHO-functional class III patients because of its survival benefits.<br>• Continuous intravenous epoprostenol is recommended as first-line therapy for WHO-functional class IV PAH patients because of the survival benefit in this subset. Subcutaneous and intravenous treprostinil are also FDA-approved for the treatment of WHO-functional class IV patients.<br>• Although ambrisentan, bosentan, and sildenafil are approved in WHO-functional class IV patients, only a small number of these patients were included in the randomized controlled trials of these agents. Therefore, most experts consider these treatments as a second line in severely ill patients.<br>• In WHO-functional class IV patients, initial combination therapy should also be considered. In the case of inadequate clinical response, sequential combination therapy should be considered.<br>• Combination therapy can include an ERA plus a PDE-5 inhibitor, a prostanoid plus an ERA, or a prostanoid plus a PDE-5 inhibitor.<br>• Balloon atrial septostomy and/or lung transplantation are indicated for PAH with inadequate clinical response despite optimal medical therapy or where medical treatments are unavailable. |

*This document was developed in collaboration with the American College of Chest Physicians, American Thoracic Society, and the Pulmonary Hypertension Association.
†This document was endorsed by the International Society of Heart and Lung Transplantation.

## Conclusions

Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis. There are four classes of drugs that are used in the management of PAH, including prostanoids, endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors and soluble guanylate cyclase stimulators.[10] Iloprost (Ventavis®) and treprostinil (Tyvaso®) are prostanoids and are available as inhalation solutions.[1,6] Additional prostanoid products are available for intravenous or subcutaneous administration. Ambrisentan (Letairis®), bosentan (Tracleer®) and macitentan (Opsumit®) are ERAs and are available orally. Both sildenafil (Revatio®) and tadalafil (Adcirca®) are PDE-5 inhibitors and are also available orally.[2-5] Sildenafil is also available for intravenous administration.[12] Currently, sildenafil tablets are available generically.[9] Riociguat (Adempas®) is the first agent within the novel class of soluble guanylate cyclase stimulators and it is currently available orally.[8]

Clinical trials have demonstrated the safety and efficacy of the PAH agents; however, there are no head-to head trials comparing the agents within classes or between classes. The national and European consensus guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA as first-line agents in patients who are considered lower risk and are not candidates for calcium-channel blockers.[10,13,14] In patients at higher risk and with poor prognostic indexes, parenteral therapy with prostanoids should be considered first-line treatment. Epoprostenol is the preferred treatment for the most severely ill patients

and is the only therapy shown to prolong survival; however, its use may be limited by its requirement of being continually infused intravenously.[10] Treatment guidelines have not yet been updated to address the potential place in therapy for the soluble guanylate cyclase stimulators.[10,13,14]

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