



BlueCross BlueShield  
of Kansas City

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Blue Cross and Blue Shield Association

## Advanced Therapies for Pharmacological Treatment of Pulmonary Arterial Hypertension

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### **Policy**

BCBSKC will provide coverage for the pharmacologic treatment of pulmonary arterial hypertension (PAH) with prostacyclin analogues, endothelin receptor antagonists, or phosphodiesterase type 5 (PDE5) inhibitors when it is determined to be medically necessary because the following criteria are met. Conventional pharmacologic therapies are considered in all patients with PAH regardless of the etiology.

### **When Policy Topic is covered:**

The following therapies may be considered **medically necessary** for the treatment of pulmonary arterial hypertension (PAH/ WHO Group 1):

- epoprostenol sodium (FLOLAN<sup>®</sup>) continuous IV infusion;
- treprostinil sodium (REMODULIN<sup>®</sup>) Continuous SC infusion, IV infusion or (TYVASO<sup>®</sup>) inhalation via nebulizer;
- Iloprost (VENTAVIS<sup>®</sup>) Inhalation via nebulizer;
- bosentan (TRACLEER<sup>®</sup>) oral;
- ambrisentan (LETAIRIS<sup>®</sup>) oral;
- sildenafil citrate (REVATIO<sup>®</sup>) oral
- tadalafil (ADCIRCA<sup>®</sup>) oral
- vardenafil (LEVITRA<sup>®</sup>) oral

Combination therapy for the treatment of pulmonary arterial hypertension (PAH/ WHO Group 1) may be considered **medically necessary** when all of the following conditions are met:

- Patients have failed to demonstrate an adequate response to a single medication;
- Medications are from different therapeutic classes;
- Each medication may be considered medically necessary for the treatment of PAH (see above statement).

Treatment with epoprostenol requires 3 steps as follows:

- Initial dose-ranging study, which is typically performed as an inpatient. The pulmonary capillary wedge pressure is monitored, and the infusion rate of the drug is increased until dose-limiting pharmacologic effect such as nausea, vomiting, or headache is elicited. Some practitioners may consider the initial dose-ranging study optional.
- Insertion of central venous catheter and attachment to portable infusion pump. Since rebound pulmonary hypertension may recur if the drug is abruptly withdrawn, the drug labeling advises that all patients should have access to a backup infusion pump and intravenous infusion set.
- Ongoing maintenance of portable infusion pump and treatment of complications related to the pump. Complications include catheter thrombosis, sepsis, and pump malfunction. In the clinical

trials, a cold pouch and frozen gel packs were used to facilitate extended use at ambient temperatures.

Treatment with iloprost requires the use of a specialized dispensing device.

### **When Policy Topic is not covered:**

Combination therapy as first-line treatment is considered **investigational**.

The use of epoprostenol, treprostinil, iloprost, bosentan, ambrisentan, sildenafil, tadalafil and vardenafil is considered **investigational** for the treatment of non-PAH PH conditions (WHO Groups 2-5), including but not limited to;

- Pulmonary hypertension associated with left heart diseases;
- Pulmonary hypertension associated with lung diseases and/ or hypoxemia (including chronic obstructive pulmonary disease);
- Pulmonary hypertension due to chronic thrombotic and/or embolic disease;
- Miscellaneous group (i.e., sarcoidosis, histiocytosis X and lymphangiomatosis)

### **Considerations**

This Blue Cross and Blue Shield of Kansas City policy statement is consistent with the Blue Cross and Blue Shield Association Policy 5.01.09

### **Description of Procedure or Service**

Pulmonary hypertension refers to the presence of abnormally high pulmonary vascular pressure; a subset of patients are considered to have pulmonary arterial hypertension (PAH), a rare and debilitating disease associated with progressive right ventricular dilation and low cardiac output. Several advanced therapies, including prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 (PDE5) inhibitors, are available to treat PAH. Combination advanced therapy has also been proposed.

### **Background**

Pulmonary hypertension (PH) refers to the presence of abnormally high pulmonary vascular pressure. The World Health Organization (WHO) classifies patients with PH into 5 groups based on the etiology of the condition. These groups differ in their clinical presentation, diagnostic findings, and response to treatment: Group 1, pulmonary arterial hypertension (PAH) includes disorders in which the PH is associated with the pulmonary artery. The classification of pulmonary arterial hypertension (Group 1) devised in 2003 following the 3<sup>rd</sup> World Symposium on Pulmonary Arterial Hypertension, is as follows (1):

1. Pulmonary arterial hypertension (PAH)
  1. Idiopathic (IPAH)
  2. Familial (FPAH)
  3. Associated with (APAH):
    1. Connective tissue disorder
    2. Congenital systemic-to-pulmonary shunts
    3. Portal hypertension
    4. HIV infection
    5. Drugs and toxins
    6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
  4. Associated with significant venous or capillary involvement:
    1. Pulmonary veno-occlusive disease (PVOD)

2. Pulmonary capillary hemangiomatosis (PCH)
5. Persistent pulmonary hypertension of the newborn

In 2009, based on the consensus of an international group of experts at the 4<sup>th</sup> World Symposium on Pulmonary Hypertension, modifications to the classification of pulmonary hypertension were proposed. A key difference from the ACCF/AHA [ACC Foundation/American Heart Association] classification is the introduction of a new category of PH, called “Group 1 prime” and defined as pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH). The ACCF/AHA nomenclature lists these conditions as sub-categories of Group 1. The updated classification of Group 1 PAH, with key changes in **bold**, is as follows (1):

1. Pulmonary arterial hypertension (PAH)
  1. Idiopathic (IPAH)
  2. **Heritable**
    1. **BMPR2**
    2. **ALK1, endoglin (with or without hereditary hemorrhage telangiectasia)**
    3. **Unknown**
  3. Drug and toxin-induced
  4. Associated with:
    1. Connective tissue disorder
    2. HIV infection
    3. Portal hypertension
    4. Congenital heart diseases
    5. **Schistosomiasis**
    6. **Chronic hemolytic anemia**
5. Persistent pulmonary hypertension of the newborn

### **1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PHC)**

Pulmonary arterial hypertension (PAH) is a rare and debilitating disease characterized by abnormal proliferation and contraction of pulmonary artery smooth muscle cells. This condition causes a decrease in the size of the pulmonary artery lumen, a decreased reactivity of the vascular bed, increased pulmonary vascular resistance (PVR), and elevated pressure in the pulmonary circulation (initially with normal left-sided pressures) and leads to overload-induced progressive right ventricular dilation and low cardiac output.

Idiopathic pulmonary hypertension (IPAH) is the most common type of PAH and is more prevalent in women than in men. Familial PAH often results from a mutation in bone morphogenetic protein receptor-2 (BMPR2) and is inherited as an autosomal dominant disease. PAH is also associated with congenital heart disease, connective tissue diseases, drugs and toxins, human immunodeficiency virus (HIV), portal hypertension, hemoglobinopathies, and myeloproliferative disorders. The diagnosis of PAH requires confirmation with a complete right heart catheterization. The current hemodynamic definition of PAH is a mean pulmonary artery pressure greater than 25 mm Hg; a pulmonary capillary wedge pressure, or left ventricular end-diastolic pressure less than or equal to 15 mm Hg; and a pulmonary vascular resistance greater than 3 Wood units.

#### *Baseline Assessment of PAH*

A baseline assessment to determine severity of PAH is often performed before initiation of therapy.

This assessment includes the following measures as key determinants of disease severity;

Functional impairment: The functional significance of PAH is determined by measuring exercising capacity and determining New York Heart Association (NYHA) or WHO functional class. The WHO functional classification recognizes the importance of near syncope and syncope. Syncope is thought to worsen the prognosis in patients with PAH. Although not explicitly stated, PAH patients who have experienced a syncopal episode are generally assigned to WHO functional class IV.

### **The New York Heart Association (NYHA) Classification- functional classification**

Class I patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II patients with slight, mild limitation of activity; they are comfortable with rest or mild exertion.

Class III patients with marked limitation of activity; they are comfortable only at rest

Class IV patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

### **World Health Organization (WHO)- functional classification for pulmonary arterial hypertension**

Class I no limitation of clinical activity; ordinary physical activity does not cause dyspnea or fatigue

Class II slight limitation in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest

Class III marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest

Class IV unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity

Hemodynamic derangement: pulmonary artery systolic pressure and right ventricular function can be estimated by echocardiography. Right heart catheterization is performed to accurately measure the hemodynamic parameters and confirm PAH. Right heart catheterization is often deferred until advanced therapy is indicated because it is an invasive procedure. Patients with PAH typically undergo an invasive hemodynamic assessment and an acute vasoreactivity test prior to the initiation of advanced therapy. The acute vasoreactivity test involves administration of a short-acting vasodilator, then measuring the hemodynamic response with a right heart catheter. Agents commonly used include epoprostenol, adenosine, and inhaled nitric oxide. An acute vasoreactivity test is considered positive if mean pulmonary artery pressure decreases at least 10 mm Hg and to a value less than 40 mm Hg, with an increased or unchanged cardiac output and a minimally reduced or unchanged systemic blood pressure. Patients with a positive vasoreactivity test are candidates for a trial of calcium channel blocker therapy. In contrast, patients with a negative vasoreactivity test should be treated with alternative agents; calcium channel blockers (CCBs) have not shown to be beneficial in these patients and may be harmful.

### *Medical Management of PAH*

Conventional therapies are considered in all patients with PAH regardless of the etiology; diuretics, oxygen therapy, anticoagulants, digoxin, and exercise. Digoxin has been shown to have beneficial effects when used with caution (i.e., patients may be at higher risk for digitalis toxicity and require close monitoring). Patients with a positive vasoreactivity test can be given a trial of CCBs. Patients with a negative vasoreactivity test require advanced therapy with prostacyclin analogues, endothelin receptor antagonists, or phosphodiesterase type 5 (PDE5) inhibitors. Various combinations of treatments have also been suggested. Lung transplantation and combined heart-lung transplantation have been

performed in patients who are refractory to medical management. Objective assessments to measure treatment response include improvement in exercise capacity (6-minute walk test [6MWT], cardiopulmonary exercise test, treadmill test), hemodynamics, and survival.

The following table summarizes the advanced therapies for treatment of PAH (WHO Group 1) and their regulatory status:

<b>Advanced Therapy</b>		
<b>Drug</b>	<b>Route(s) of Administration</b>	<b>FDA Approved Indications</b>
<b>Brand Name</b>	<b>Dose range</b>	
<b>Manufacturer</b>		
<b>FDA approval date</b>		
<b>Prostacyclin Analogues</b>		
epoprostenol sodium (FLOLAN®) GlaxoSmithKline FDA approved 1995	Continuous intravenous (IV) infusion via central venous catheter using an ambulatory infusion pump 1 to 20 ng/kg/min	Long-term treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA Class III and Class IV patients who do not respond adequately to conventional therapy.
treprostinil sodium (REMODULIN®) United Therapeutics Corp. FDA approved 2002	Continuous subcutaneous (SC) infusion IV infusion 0.625 to 1.25 ng/kg/min	Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with NYHA Class II-IV symptoms, to diminish symptoms associated with exercise. Patients who require transition from Flolan, to reduce the rate of clinical deterioration.
(TYVASO®) United Therapeutics Corp. FDA approved 2009	Inhalation via nebulizer; specific to one pulmonary drug delivery system 18-54 mcg, 4 times/day	Treatment of PAH in patients with NYHA Class III symptoms, to increase walk distance.
iloprost (VENTAVIS®) Actelion, Ltd. FDA approved 2004	Inhalation via nebulizer; either of two pulmonary drug delivery devices 2.5 to 5 mcg, 6-9 times/day	Treatment of PAH in patients with NYHA Class III or IV symptoms.
beraprost NOT APPROVED IN US & EU Failed reviews Approved in Japan for treatment of PAH	oral	No FDA-approved indications for PAH.
<b>Endothelin Receptor Antagonists</b>		
bosentan (TRACLEER®) Actelion, Ltd. FDA approved 2001	Oral 62.5 to 125 mg 2 times/day	Treatment of PAH in WHO Class III or IV symptoms to improve exercise ability and decrease rate of clinical worsening
ambrisentan (LETAIRIS®) Gilead Sciences, Inc. FDA approved 2007	Oral 5-10 mg/day	Treatment of PAH in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening

<b>Phosphodiesterase (PDE5) Inhibitors</b>		
sildenafil citrate (REVATIO®) Pfizer Labs FDA approved 2005	Oral 20 mg 3 times/day	Treatment of PAH to improve exercise ability August 2012: FDA recommended that Revatio not be prescribed to children (ages 1-17) for PAH. (The product has not been approved for the treatment of PAH in children).
tadalafil (ADCIRCA®) Eli Lilly FDA approved 2009	Oral 40 mg once/day	Treatment of PAH to improve exercise ability
vardenafil (LEVITRA®) FDA approved (but not for PAH)	Oral	No FDA-approved indications for PAH. One randomized trial outside of U.S.

It is important to emphasize that the approved treatments for pulmonary arterial disease (PAH; WHO Group 1) have serious side effects and have not shown to be effective in patients with other forms of pulmonary hypertension.

### **Rationale**

This policy was originally created in 1998 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed for the period March 2011 through July 2012. Following is a summary of the key literature to date on agents that are approved by the U.S. Food and Drug Administration (FDA) for treatment of pulmonary arterial hypertension (PAH/WHO (World Health Organization) Group 1).

### **Monotherapy using prostanoids, endothelin-receptor antagonists or phosphodiesterase type-5 (PDE5) inhibitors**

Several meta-analyses that pool the findings of studies evaluating the efficacy of PAH treatments have been published. In 2009, Galie and colleagues in Italy published a meta-analysis of randomized controlled trials (RCTs) examining approved medications i.e., prostanoids, endothelin-receptor antagonists, and phosphodiesterase type-5 (PDE5) inhibitors for treating PAH. (2) The primary analysis included only studies with a placebo-comparator arm; a sensitivity analysis also included studies comparing 2 active treatment arms. The main outcome measure was all-cause mortality. Twenty-one trials were included in the primary analysis (n=3,140), and 2 additional studies (n=59) were included in the sensitivity analysis. Average duration of the trials was 14.3 weeks. All-cause mortality rate in the control group was 3.8%. Active treatments were associated with a reduction in mortality of 43%; the sensitivity analysis confirmed a reduction in mortality of 38%. The authors concluded that the results of this meta-analysis suggest an improvement of survival in the patients treated with the targeted therapies approved for PAH. The limitations of the meta-analysis include the prolonged period of time between the first and last RCT (about 18 years), the different duration of the trials (ranging from 8–36 weeks), the lack of blinding in some studies, the pooling of multiple active treatment arms, and potential heterogeneity in the conduct of the trials. The meta-analysis included studies with compounds that were eventually not approved because of lack of efficacy and different doses of approved therapies that were not approved because they were less effective or had increased adverse effects.

Two meta-analyses published in 2010, were similar in scope and design to the 2009 meta-analysis by Galie and colleagues. (2) All 3 were limited to RCTs in patients with PAH, had all-cause mortality as the primary outcome and evaluated the same classes of medications, prostanoids, endothelin receptor antagonists, and PDE5 inhibitors. Ryerson and colleagues searched the literature through November 2009. (3) Their eligibility criteria included RCTs in adults with PAH, and they further required that studies have a follow-up of at least 8 weeks, be double-blind, and be placebo-controlled (except for

studies on intravenous [IV] medication use). They included both studies that compared one medication to placebo (monotherapy), as well as studies that added a second medication versus placebo to a baseline medication (combined treatment); the latter were categorized by the class of the medication in the study that was under investigation. Twenty-four trials met the inclusion criteria. This included 11 on prostanoids, 8 on endothelin-receptor antagonists, and 3 on PDE5 inhibitors. The investigators did not pool studies across classes of medications. There was a statistically significant reduction in all-cause mortality in a meta-analysis of the studies on prostanoids, but not studies on endothelin-receptor antagonists, or PDE5 inhibitors. The pooled analysis of prostanoid trials found a 51% mortality reduction (95% confidence interval [CI]: 18-71%). Meta-analyses of each of the 3 classes of medication found statistically significant improvement in exercise capacity, the primary outcome in most of the studies. In pooled analyses, prostanoids were associated with a mean placebo-corrected improvement in 6-minute walk distance of 29 meters (95% CI: 18-41 meters), endothelin-receptor antagonists were associated with improvement of 38 meters (95% CI: 27 to 49 meters), and PDE5 inhibitors were associated with an improvement of 34 meters (95% CI: 23-49 meters).

The other 2010 meta-analysis, by Macchia and colleagues, searched the literature through April 2009 and, like the Ryerson et al. study, included RCTs on adults with PAH. (4) However, in this study, both open and blinded trials were included, and eligibility was not limited by type of control group (e.g. placebo). Combination medication studies were treated in the same manner as in Ryerson et al., discussed above. Twenty-six trials met eligibility criteria. Of these, 9 were on prostanoids, 8 on endothelin receptor antagonists, and 8 on PDE5 inhibitors. In a meta-analysis of studies on all 3 classes of medications combined (23 studies), there was a statistically significant reduction in total mortality of 39% (2-62%) in the treatment group compared to controls. However, when studies on each class of medication were examined separately, there were no significant reductions in mortality. For example, the pooled analysis of studies on prostanoids found a nonsignificant 34% reduction in mortality; the 95% CI was consistent with a 64% decrease in mortality to a 21% increase. The mortality reduction seemed confined to studies with more seriously ill study populations. With all classes of medication combined, there was a significant reduction in all-cause mortality when findings from trials with a median mortality of above 2% were pooled; mortality reduction was 49% (95% CI: 12-70%). There was no significant reduction in mortality in studies that had lower mortality rates. In addition, there was a significant mortality reduction in studies that included patients with functional class IV (42%, 95% CI: 4-65%) but not studies that excluded these patients. The authors also pooled study findings on change in exercise capacity and pulmonary vascular resistance (PVR). They found small but statistically significant improvement in exercise capacity and PVR. This was true for analyses pooling all studies, as well as those limited to one class of medication. For example, a pooled analysis of endothelin receptor antagonists found a mean increase in the 6-minute walk distance of 46 meters (95% CI: 38-54 meters) with treatment versus control. A meta-analysis of prostanoid studies found a mean fall in PVR of 4.24 mm Hg (95% CI: fall of 3.49-5.00 mm).

The all-cause mortality reduction with all medications combined in the Macchia et al. (2010) meta-analysis, 39%, is similar to that found by Galie et al. (2009), 43%. Macchia and colleagues, however, urge caution when interpreting this finding, since none of the individual classes of medication were found to reduce mortality. Moreover, they question the validity of combining studies of pharmacologic treatments that have completely different modes of action and suggest that the finding of mortality reduction be tested in prospective clinical trials.

Editorial critiques of the available literature raise questions about the study endpoints selected, which are often short-term measures that are insufficient for addressing the mechanism of disease, optimizing treatment by patient population, and making meaningful comparisons between therapies. Studies are short in duration and compare outcomes that reflect symptomatic improvement (e.g., 6-minute walk distance or functional class) but not disease status (such as vasculature remodeling) or survival. Studies also need to address the durability of these outcomes. However, designing long-term (1 year or more) studies with survival as an endpoint may raise additional issues, including potential ethical questions.

Representative randomized trials and observational studies evaluating specific medications are described below.

### *Epoprostenol*

The original approval of epoprostenol from the FDA was based on a 12-week trial of 81 patients with New York Heart Association (NYHA) Class III or Class IV primary pulmonary hypertension who were randomized to receive either epoprostenol or conventional medical management. (5) As compared to conventional therapy, the continuous intravenous infusion of epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe primary pulmonary hypertension. In 1998, McLaughlin and colleagues reported on a case series of 27 patients treated with epoprostenol who were followed up for a mean of 16 months. (6) All patients had improvements in symptoms such as NYHA classification and exercise duration. While pulmonary vascular resistance declined only 23% acutely in response to a test dose of adenosine (another vasodilator), over long-term follow-up the vascular resistance fell by 53%. These results suggest that the beneficial effects of epoprostenol are not solely related to vasodilation but perhaps are related to anticoagulant and endothelial cytoprotective effects. McLaughlin and colleagues subsequently reported survival data for those receiving epoprostenol. (7) A total of 162 consecutive patients diagnosed with primary pulmonary hypertension (PHTN) were treated with epoprostenol and followed up for a mean of 36.3 months. Observed survival at 1, 2, and 3 years was 87.8%, 76.3%, and 62.8%, which was significantly greater than the expected survival of 58.95, 46.3%, and 35.4%, all respectively, based on historical controls.

In 2000, epoprostenol received additional FDA approval as a treatment for pulmonary hypertension (PH) associated with the scleroderma spectrum of disease, based in part on the following data. Humbert and colleagues reported on an uncontrolled case series of epoprostenol in 17 patients with PHTN associated with either scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), or Sjogren's syndrome. (8) Patients were followed up from 14 to 154 weeks. After 6 weeks, exercise capacity improved in 15 of 17 patients; the remaining 2 patients died of pulmonary edema or sepsis. During the long-term follow-up, an additional 5 patients died, 2 patients underwent successful lung transplantation, and 7 of the remaining 8 patients had a persistent clinical improvement. Badesch and colleagues reported on a study that randomized 111 patients with PH related to scleroderma to receive either conventional therapy or conventional therapy in addition to epoprostenol therapy. (9) The primary outcome measure was exercise capacity. A significant improvement in exercise capacity was noted in the epoprostenol group compared to the control group, for whom exercise capacity actually decreased. Cardiopulmonary hemodynamics also improved significantly in the treatment group compared to the control group. A total of 38% of patients in the treatment group reported improvements in NYHA classification, compared to none in the control group. Four deaths occurred in the epoprostenol group compared to 5 in the control group, although it should be noted that the study was not adequately powered to detect a significant difference in survival.

Rosenzweig and colleagues reported on a case series of 20 patients with PH secondary to congenital heart disease who had failed to improve clinically with conventional therapy. (10) Although none of the patients experienced a decrease in pulmonary artery pressure in response to epoprostenol infusion, long-term therapy was associated with a 21% reduction in pulmonary artery pressure. In addition, NYHA classification improved from a mean of 3.2 to 2.0. A nonsignificant increase occurred in exercise capacity.

### *Treprostinil*

The FDA approval of treprostinil (Remodulin) was based in part on 2 randomized, placebo-controlled double-blind studies of subcutaneous infusion of treprostinil in 470 patients with PAH, either idiopathic or associated with connective tissue disease or congenital systemic-to-pulmonary shunts and a subgroup analysis of 90 patients with PAH associated with connective tissue disease. (11, 12) Endpoints, measured at 12 weeks, included exercise capacity (as measured by the 6-minute walk test

[6MWT]), dyspnea, and hemodynamic effects. There was a median 16-meter improvement in the 6MWT, which although statistically significant was not as great as that noted for epoprostenol. Patients who were more compromised at baseline had the greatest improvements, and thus the lower median improvement may be related to the inclusion of less severe patients (i.e., Class II) in this trial. There were no statistically significant differences in pretreatment and post-treatment hemodynamic variables between patients with different connective tissue diseases.

A cohort study of long-term survival was identified, which compared survival of patients (idiopathic PAH or associated with connective tissue, congenital heart disease, portal hypertension, or human immunodeficiency virus [HIV]) treated with treprostinil (up to 4 years) with predicted survival using an National Institutes of Health (NIH) registry equation or untreated patients from registry data. (13) Treprostinil survival among 860 patients was 87–68% over 1–4 years, noting that 59% of patients discontinued treatment due to adverse events (39%), death (27%), clinical deterioration (23%), and other reasons (withdrew consent, transplantation, protocol violation, and loss to follow-up; 11%). Sensitivity analyses found no differences between those discontinuing due to site pain reaction and patients who did not discontinue; however, selection bias due to censoring is possible and could bias the results in favor of treprostinil survival. Among 332 patients for whom predicted survival could be calculated (using the NIH registry equation), treprostinil treatment resulted in 91% and 72% survival at 1 and 4 years compared to predicted survival of 69% and 38%, respectively.

Findings of a 12-week randomized placebo-controlled trial evaluating intravenous treprostinil in treatment-naïve patients with PAH were published in 2010 by Hiremath and colleagues. (14) The study, conducted in India, randomized 45 patients, one of whom died during catheter placement. Due to safety concerns, recruitment was stopped early after these 45 patients had enrolled; an intention-to-treat analysis was performed on these patients' outcomes data. Forty-two of the 44 patients who received study medication had idiopathic PAH, and 2 had PAH associated with collagen vascular disease. Forty-two of 44 patients had NYHA Class III disease and 2 had Class IV disease. The initial dose of medication was 4 ng/kg/min treprostinil or an equivalent volume of placebo. After the first week, dose increases up to 8 ng/kg/min weekly were allowed, up to a maximum of 100 ng/kg/min. Thirty-one of 45 (67%) randomized patients completed the study; 6 patients (2 in each group) died during the 12-week follow-up period. The mean treprostinil dose at 12 weeks was 72 ng/kg/min, and the mean placebo dose was 80 ng/kg/min. The primary efficacy outcome was change in the 6-minute walk distance (6MWD) from baseline to 12 weeks. The mean baseline 6MWD was 292 meters in the treprostinil group (n=30) and 231 in the placebo group (n=14). The mean change was an increase of 67.2 meters in the treprostinil group and a decrease of 25.5 meters in the placebo group; the difference between groups was statistically significant, p=0.022. This represents a placebo-corrected difference of a mean of 92.7 meters (standard error [SE]=42.0). The median placebo-corrected difference between groups was 83 meters (95% confidence interval [CI]:7-187 meters, p=0.008) There were also statistically significant differences on other outcomes, favoring the treprostinil group. For example, there was a mean decrease of 1.7 points on the Borg dyspnea scale in the treprostinil group and a mean increase of 0.4 points in the placebo group, p=0.009. (A higher score on the Borg scale represents more dyspnea.)

### *Iloprost*

The FDA approval of iloprost (i.e., Ventavis) was based in part on the results of a randomized, double-blind, multicenter placebo-controlled trial conducted in 203 adult patients with PAH (WHO Group I); idiopathic (53%), associated with connective tissue disease including CREST and scleroderma (17%), or associated with anorexigen use (2%) or pulmonary hypertension related to chronic thromboembolic disease (WHO Group IV; 28%). (15) The primary endpoint was a composite endpoint at 12 weeks defined by 1) improvement in exercise capacity (6MWT) and 2) improvement by at least 1 NYHA class versus baseline; and no death or deterioration of pulmonary function. The response rate was 19% for the iloprost group compared to 4% for the placebo group. There was inadequate evidence of benefit in patients with PH associated with chronic thromboembolic disease (WHO Group IV). The use of iloprost requires a specialized dispensing device. One limitation of this delivery system is that the drug may be lost in the device tubing.

### *Bosentan*

The FDA approval of bosentan (Tracleer) was based in part on a randomized, placebo-controlled double-blind study of 213 patients with PAH (idiopathic (70%) or associated with connective tissue disease (30%); WHO Group I). (16) The primary endpoint was degree of change in exercise capacity. At 16 weeks, a significant improvement was found in the 6MWT in the treatment group compared to the placebo group. Other measures of symptoms and functional status also improved in the treatment group, including a composite measure of “clinical worsening,” which consisted of the outcomes of death, hospitalizations for PHTN, discontinuation of therapy, or need for epoprostenol. In addition, the treatment group had a significant increase in cardiac index associated with reduction in the pulmonary artery pressure. A review article detailed 2 RCTs (n=310) that evaluated the effect of bosentan for the treatment of systemic sclerosis-associated digital ulcers. In both trials, there was significant improvement in hand function; however, no differences were seen in healing of established ulcers. (17)

### *Ambrisentan*

The FDA approval of ambrisentan (Letairis) was based on two 12-week randomized, double-blind, placebo-controlled multicenter studies of 393 patients with PAH. (18) ARIES-1 compared once-daily doses of 5 mg and 10 mg of ambrisentan to placebo, while ARIES-2 compared once-daily doses of 2.5 and 5 mg. Patients were not taking any of the other agents discussed in this policy during the study. Sixty-four percent had idiopathic PHTN, and 32% had PHTN associated with connective tissue disease. Placebo-adjusted mean changes from baseline in the 6MWD were 51 meters in ARIES-1 and 59 meters in ARIES-2 (results for the higher dosages). For the two trials, clinical worsening was noted in 10% and 22% of the placebo patients compared to 3% and 6% - all respectively, of those receiving ambrisentan. In 2010, Blalock published long-term outcomes in 12 of 14 patients who were enrolled in the ARIES-1 study at a single institution; these patients enrolled in an extension of the 12-week randomized period in which all participants received ambrisentan. (19) All of the 12 patients remained on ambrisentan monotherapy during the first 2 years of follow-up. Two patients developed worsening symptoms requiring add-on intravenous (IV) therapy toward the end of the second year; 2 others developed worsening symptoms after 2 years and began IV therapy. At last follow-up (3.5 to 5 years), 11 patients remained alive; 3 were on ambrisentan monotherapy, 5 on combinations of oral therapies and 2 on ambrisentan plus an IV prostacyclin.

### *Sildenafil citrate*

The FDA approval of sildenafil citrate (Revatio, also marketed as Viagra) was based in part on the results of a study that randomized 278 patients with PAH (idiopathic [60%], connective tissue disease [40%] WHO Group 1) to receive either placebo or sildenafil (20, 40, or 80 mg), orally, 3 times daily for 12 weeks. (20) The study is known as the SUPER-1 trial and findings were published by Galie and colleagues in 2005. There was a significant improvement in primary endpoint, defined as the change in baseline to week 12 in the distance walked in 6 minutes (6MWD). Of the 222 patients completing 1 year of treatment, the improvement in distance walked in 6 minutes was 51 meters. There was no significant difference among the 3 different doses of sildenafil given, and thus the recommended dose is 20 mg 3 times per day. At doses higher than the recommended dose, there was greater incidence of some adverse events including flushing, diarrhea, myalgia, and visual disturbances.

In 2011, Rubin and colleagues published findings from an open-label extension study for which all patients who completed the initial trial were eligible (SUPER-2). (21) In the extension study, all patients titrated up to 80 mg sildenafil three times daily unless they could not tolerate this dose; there was no placebo group. A total of 259 of the 277 (93.5%) patients in the SUPER-1 trial entered the extension study. Compared to their SUPER-1 baseline value, at 3 years, 127 of 277 (46%) of patients had increased their 6MWD, 49 (18%) decreased their 6MWD, and 48 (17%) had missing data. A total of 81 patients (29%) had at least a 60-meter improvement in the 6MWD compared to the SUPER-1 baseline, and another 22 (8%) had a 30- to 60-meter improvement. Three years from SUPER-1 baseline, 187

patients were alive, 53 had died, and 37 were lost to follow-up. The Kaplan-Meier estimate of the survival rate, based on all randomized patients, was 79%. The estimate of survival was 68% if all censored patients were considered to have died. During the extension study, most adverse effects were mild or moderate in severity and were consistent with known side effects of sildenafil e.g., headache, diarrhea, and dyspepsia. Serious adverse events were reported by 153 of 277 (55%) patients. Serious events that were perceived to be treatment-related included grand mal seizure, hypotension, drug hypersensitivity, and gastroesophageal reflux disease (exact numbers of affected patients were not reported). Thirty-nine patients discontinued drug use due to adverse events. A major limitation of the extension study in terms of its ability to evaluate efficacy was that there was no comparison group of patients who were not taking sildenafil.

### *Tadalafil*

The pivotal trial on tadalafil (ADCIRCA®), the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) study, was published by Galie and colleagues in 2009. (22) This was a double-blind multicenter study conducted in the United States, Canada, Europe, and Japan. It included 406 patients who were at least 12 years-old and had symptomatic PAH (Group 1) that was idiopathic/heritable or related to anorexigen use, connective tissue disease, HIV infection or congenital systemic-to-pulmonary shunts. Randomization was stratified by type of PAH (idiopathic/heritable and anorexigen use versus other types), baseline bosentan use (53% were using bosentan), and baseline walking distance (less than 325 meters or at least 325 meters). Patients were assigned to receive 16 weeks of treatment with placebo (n=82) or 1 of 4 doses of tadalafil: 2.5 mg (n=82), 10 mg (n=80), 20 mg (n=82), or 40 mg (n=79). A total of 331 (82%) patients completed the 16-week study. Discontinuation rates were similar across all treatment groups, about 16% in each. The efficacy analysis was intention-to-treat and included 405 patients (all those randomized minus 1 patient who did not receive study medication). The primary efficacy outcome was placebo-corrected change from baseline to 16 weeks in the 6MWD. Compared to placebo, only the patients receiving 40 mg tadalafil significantly improved their 6MWD (i.e., the p value was less than the prespecified cutoff of 0.01). For the 392 participants who were assessed at 16 weeks, change in placebo-corrected 6MWD was as follows: 14 meters (95% CI: 6-33) for the 79 patients in the 2.5-mg group, 20 meters (95% CI: 1-39) for the 78 patients in the 10-mg group, 27 meters (95% CI: 11-44) for the 82 patients in the 20-mg group, and 33 meters (95% CI: 15-50) in the 79 patients in the 40-mg group. The statistical significance cutoff for secondary outcomes was 0.05. There were no statistically significant differences between any of the tadalafil groups and placebo in the proportion of patients with improved WHO functional class and change in the Borg dyspnea scales. Time to clinical worsening, however, significantly improved in the tadalafil 40-mg group compared to placebo (p=0.041). Moreover, the 40-mg group had significantly greater improvement than placebo in 6 of the 8 quality-of-life domains in the Medical Outcomes Study 36-item short form (SF-36); the total quality-of-life score was not reported. Three deaths occurred during the 16-week study period; the study was not designed to evaluate differences in the mortality rate.

### *Vardenafil*

Jing and colleagues published 2 studies from China evaluating vardenafil (LEVITRA®); a case series in 2009 and an RCT in 2011. The case series included 45 patients with PAH who were admitted for treatment at one of the participating study centers. (23) Eligibility was limited to patients with idiopathic PAH, advanced pulmonary vasculopathy associated with connective tissue disease and congenital heart disease or portopulmonary hypertension. Patients were treated with oral vardenafil 5 mg daily for 1 month, after which time the dose was increased to 10 mg daily (5 mg twice a day) if tolerated. None of the patients had received other PAH-active drugs in the previous 3 months, but patients had been using vardenafil for a mean of 14 months before study entry. The mean baseline 6MWD was 409 meters (standard deviation [SD]: 103). All patients were evaluated after 3 months of treatment at which time the 6MWD had increased a mean of 71 meters (SD: 78). The change in distance from baseline was statistically significant (p<0.001). All patients were also evaluated after a mean of 14 months (SD: 3) of treatment. At this longer-term follow-up, the mean 6MWD was 83 meters (SD: 92), which was significantly higher than baseline (p<0.001) but not higher than the distance walked at 3 months

( $p=0.36$ ). Change in functional improvement was seen at both 3 months and 14 months. At baseline, 11 (24%) patients were in WHO functional class II, 29 (64%) were in class III, and 5 (12%) were in class IV. At the end of the study, 5 (11%) were in functional class I, 31 (69%) in class II, 8 (18%) in class III, and 1 (2%) in class IV. No patients died during the study; 2 patients were admitted to the hospital for PAH-related symptoms after 6 and 11 months, respectively. The study was limited in that there was no comparison group, the sample size was small, and most patients had previously received the study medication so they were more likely to continue to respond to it.

A double-blind RCT, published by Jing and colleagues in 2011, was conducted at 8 centers in mainland China. (24) The study randomized 66 patients to receive 12 weeks of oral vardenafil monotherapy ( $n=44$ ) compared to placebo ( $n=22$ ). Patients in the active treatment group received 5 mg vardenafil once daily for the first 4 weeks and then increased to the target dose of 5 mg twice daily, if tolerated. Two patients dropped out before any follow-up data were recorded. Thirty-nine of the remaining 64 patients (61%) had idiopathic PAH, 19 (30%) had connective tissue disease, and 6 (9%) had repaired right-to-left shunting. WHO functional class at baseline was class II in 30 (47%) and class III in 34 (52%). Baseline 6MWD (the primary efficacy outcome) was a mean of 388 meters in the placebo group and 395 in the vardenafil group. A total of 59 patients (89% of those randomized) completed the 12-week randomized phase. After 12 weeks, the median 6MWD increased by 59 meters in the vardenafil group and decreased by 10 meters in the placebo group. The mean placebo-corrected treatment effect was 69 meters (95% CI: 41 to 98 meters,  $p<0.001$ ). During the 12-week follow-up period, 1 of 44 (2%) in the vardenafil group and 4 of 22 (18%) experienced clinical worsening; the difference between groups was statistically significant,  $p=0.044$ . This includes 2 patients in the placebo group who died. Other clinical outcomes favored the treatment group. Ten of 44 (23%) patients treated with vardenafil improved at least one WHO functional class, compared to only 1 of 22 (5%) of patients in the placebo group. In addition, the mean Borg dyspnea scale improved at week 12 (mean decrease of 0.4 point) in the vardenafil group, whereas the dyspnea score worsened (increase of 1.8 points) in the placebo group; the authors did not report a between-group  $p$  value. Fifty-eight patients completed a 12-week open-label extension of the study in which all patients received vardenafil 5 mg twice a day. At the end of the extension phase, the mean improvement in the 6MWD in the group originally assigned to vardenafil was 69 meters. In addition, patients who had been in the placebo group and then took vardenafil for 12 weeks had a mean increase of 59 meters in walk distance from week 12 (mean of 49 meters improvement from baseline). This remains the only published RCT evaluating vardenafil for PAH; no major study was conducted in the United States; a limitation is that the analysis was not intention-to-treat.

Conclusions: RCTs and several meta-analyses of randomized controlled trials have found that prostanoids, endothelin receptor antagonists, and phosphodiesterase type-5 inhibitors are all associated with small but statistically significant improvement in exercise capacity and hemodynamic parameters in patients with PAH. Findings on mortality reduction are mixed; in general, the evidence base on the effect of approved treatments on mortality is limited by the small size and short duration of most trials

### **Combination Therapy**

Randomized controlled trials have evaluated various combinations of medications for treating PAH. In addition, meta-analyses of RCTs have been published. The meta-analyses considered various combinations of medications; all of the individual trials included in the meta-analyses used medications from different classes. In addition, all trials used combination therapy as second-line treatment, i.e., patients were already taking one medication when they entered the trial.

A meta-analysis published by Fox and colleagues in 2011 included 6 trials. (26) The review's inclusion criteria included studies in which patients on one active treatment were randomized to receive a second medication or placebo. In addition, studies needed to have at least 12 weeks of follow-up and to include clinical outcomes. A pooled analysis of data from 4 trials found a statistically significant increase in the

6MWD with combination therapy versus monotherapy (weighted mean difference [WMD]: 25.2 meters, 95% CI: 13.3 to 38.2). The clinical significance of this degree of difference between groups in the 6MWD is unclear. Other pooled analysis did not find significant differences between groups. A meta-analysis of data from 4 trials did not find a lower risk of mortality with combination versus monotherapy (risk ratio [RR]: 0.42, 95% CI: 0.08 to 2.26). In addition, a meta-analysis of 4 trials did not find a significant difference between groups in the rate of clinical worsening (composite variable including death, hospital admission, transplantation and treatment escalation) (RR: 0.42, 95% CI: 0.17 to 1.04).

Another meta-analysis was published by Bai and colleagues in 2011 and also included 6 trials. (27) Inclusion criteria included RCTs on treatment of adults with PAH using combination therapy, follow-up of 8 weeks or more and reporting of clinical outcomes. Five of 6 of the included articles were the same in both meta-analyses. The meta-analyses differed on the 6<sup>th</sup> article they included; one included Galie et al. (2009), (22) and the other included Barst et al. 2011. (28) However, these 2 studies reported on data from the same randomized trial. A pooled analysis of data from 5 trials found significantly greater improvement in the 6MWD with combination therapy compared to monotherapy (WMD: 22.2, 95% CI: 13.6 to 30.9). In addition, a pooled analysis of data from 5 trials found a significantly lower rate of clinical worsening with combination compared to monotherapy (RR: 0.48, 95% CI: 0.26 to 0.91). Clinical worsening referred to death, hospitalization, symptomatic deterioration, lack of improvement, interatrial fistulization, transplantation or treatment escalation. A pooled analysis of data from 5 trials did not find a significant difference between groups in the risk of mortality (RR: 0.44; 95% CI: 0.04 to 4.65).

The 2 meta-analyses both found that combination therapy resulted in significantly greater improvement in the 6MWD compared to monotherapy and both found no difference between groups in mortality. The Bai et al. meta-analysis, but not the Fox et al. meta-analysis, found a significantly lower rate of clinical worsening in the combination therapy group; clinical worsening was defined somewhat differently in the 2 meta-analyses.

The key RCTs evaluating combination treatment for PAH are described below; studies are organized according to the classes of medications that were combined.

#### *Prostacyclin analogues and endothelin receptor antagonists*

Two randomized trials evaluated the combination of inhaled iloprost and bosentan on clinical outcomes. In 2006, McLaughlin and colleagues conducted a randomized double-blind trial of adding iloprost or placebo to bosentan monotherapy in 67 patients with PAH (idiopathic, 55%, associated PAH, 45%). (29) After 12 weeks, treatment with iloprost resulted in a placebo-adjusted 6MWD improvement of 26 meters ( $p=0.05$ ). Functional class, hemodynamic parameters (e.g., pulmonary arterial pressure, -6 mm Hg vs. +3 mm Hg in the treatment and placebo groups, respectively), and time to clinical worsening ( $p=0.02$ ) were all improved at 12 weeks in the treatment group compared to the placebo group. Hoepfer et al. reported results from a small ( $n=40$ ), 12-week, non-blinded RCT evaluating the addition of iloprost to bosentan monotherapy in patients with idiopathic PAH (IPAH, WHO Group 1). (30) The study was terminated early because there appeared to be no benefit from the combined therapy: change was -10 meters on 6MWD for the combination group and no difference in functional status, VO<sub>2</sub> max, and time to clinical worsening. The study noted that these results may have been skewed by 3 patients in the iloprost group who presented with severe clinical worsening.

In 2010, McLaughlin and colleagues evaluated the addition of inhaled treprostinil to oral therapy in a double-blind RCT with 235 patients with PAH. (31) Patients had been on a stable dose of bosentan ( $n=165$ ) or sildenafil ( $n=70$ ) for at least 3 months. They were randomized to receive inhaled treprostinil sodium (up to 54 ug) or placebo 4 times daily as add-on therapy. A total of 212 (90%) patients completed the study; analysis was intention to treat. The primary efficacy outcome was change in 6MWD over 12 weeks. Mean baseline 6MWD was 346 meters in the inhaled treprostinil group and 351 in the placebo group. After 12 weeks, the median change in peak 6MWD (10-60 minutes after nebulizer use) was 21.6 meters in the treprostinil group and 3.0 meters in the placebo group. The median

between-group difference was 20 meters (95% CI: 8.0 to 32.8),  $p=0.004$ . When the analysis was limited to the patients taking bosentan at baseline, the median difference in change in 6MWD over 12 weeks was 25 meters,  $p=0.002$ . There were no differences between groups in the secondary endpoints rate of clinical worsening, Borg dyspnea scores, change in NYHA functional classifications or PAH signs and symptoms. For example, 4 of 115 (3%) patients in the treatment group and 6 of 120 (5%) in the placebo group experienced clinical worsening during the 12-week follow-up period. Another secondary outcome was quality of life, measured by the Minnesota Living with Heart Failure questionnaire (MLWHF); the potential range of the total score is 0 to 105, with a higher score indicating a worse quality of life. There was a median difference between groups of -4 points in the total score of the MLWHF; this difference was statistically significant, favoring the inhaled treprostinil group ( $p=0.027$ ). Differences between groups in the 6MWD and quality-of-life measure may not be clinically significant. Following the 12-week double-blind study, patients had the option of enrolling in an open-label extension study in which all patients received inhaled treprostinil. (32) A total of 206 of 235 (88%) patients participated in the extension study. Their mean 6MWD at baseline was 349 meters (SD: 81). The median change in 6MWD was 31 meters ( $p<0.001$ ,  $n=152$ ) at 12 months and 18 meters ( $p=0.013$ ,  $n=118$ ) at 24 months. A limitation of this analysis was that there was no comparison to patients who were not taking inhaled treprostinil.

#### *Prostacyclin analogues and phosphodiesterase inhibitors*

In the 2010 McLaughlin et al. study, discussed above, patients on monotherapy were randomized to receive added inhaled treprostinil or placebo; 70 patients were taking sildenafil at baseline. (31) In this subgroup, the median placebo-corrected change in 6MWD at 12 weeks, the primary outcome, was 9 meters; the difference between groups was not statistically significant. As previously noted, the groups did not differ significantly on secondary efficacy outcomes other than quality of life.

Simonneau and colleagues assessed the effect of adding oral sildenafil to long-term intravenous epoprostenol ( $n=267$ ) with PAH in a 2008 RCT. (33) After 16 weeks, the adjusted mean change in the 6MWD was 29.8 meters for the sildenafil group and 1.0 meter for the placebo group, a treatment difference of 28.8 meters (13.9 to 43.8 meters). In patients with IPAH, the difference between groups was 33.9 meters in favor of the sildenafil group ( $p$  value and 95% confidence interval [CI] not reported). Sildenafil also had a beneficial effect on hemodynamic measurements and health-related quality of life.

#### *Endothelin receptor antagonists and phosphodiesterase inhibitors*

An RCT by Galie and colleagues evaluated bosentan in mildly symptomatic patients; the impact of combination therapy with bosentan and sildenafil was assessed in a subgroup of patients as a secondary objective. (34) The analysis assessed the effect of bosentan versus placebo and the effect of bosentan combined with sildenafil versus placebo. There was no direct comparison between the bosentan and combination treatment groups. The sample size of this study was small. In addition, patients with IPAH and those with PAH secondary to HIV, congenital heart disease, and connective tissue disease were included. It is not clear if the same results would be expected for only those with IPAH.

The Galie et al. study on tadalafil, discussed previously, (22) included a predefined subgroup analysis comparing treatment effectiveness in patients who added tadalafil to baseline bosentan treatment and those taking only tadalafil. These findings were reported by Barst and colleagues in 2011. (28) The analysis focused on the groups assigned to 40 mg tadalafil and placebo. At 16 weeks, there was statistically significant improvement in the 6MWD among patients taking tadalafil monotherapy but not in the group taking combination therapy. The placebo-corrected 6MWD was 44 m (95% CI: 20 to 69) in the tadalafil-only group and 23 m (95% CI: -2 to 48) in patients taking the combination of tadalafil and bosentan.

Conclusions: Meta-analyses of trials on combination therapy have included studies that use medications from different classes and evaluate the addition of a second medication in patients already taking medication. Two meta-analyses, which included data from the same 6 trials, have found small, statistically significant improvement in the 6MWD and have not found a significant benefit of combination therapy on mortality. Meta-analyses had mixed findings on the impact of combination therapy on clinical worsening, depending on how this variable was defined by the authors of the meta-analysis. There are few randomized controlled trials on any particular combination of therapies and findings of these studies are mixed. The evidence is sufficient to determine that combinations of classes of medications improve exercise capacity more than a single medication, although the impact on other outcome measures is not conclusive.

### **Clinical Input Received through Physician Specialty Societies and Academic Medical Centers**

In response to requests, input was received through 4 academic medical centers while this policy was under review in 2011. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. The input focused on the issue of combination therapy. Two of the academic medical centers disagreed with the 2010 policy statement that combination therapy is considered investigational (other than when changing from one medication to another). The other two academic medical centers had mixed input; both thought there were situations in which combination therapy is medically necessary.

### **Summary**

There is evidence from multiple RCTs and meta-analyses of RCTs that monotherapy using prostanoids, endothelin-receptor antagonists or phosphodiesterase type-5 (PDE5) inhibitors improves health outcomes in patients with WHO Group 1 PAH. Thus, FDA-approved medications in these classes may be considered medically necessary for the treatment of patients with PAH. Evidence on the comparative efficacy of these individual agents is lacking; therefore it is not possible to determine which one is preferable as first-line choice for treatment.

There is evidence from 6 trials on combination therapy and meta-analyses of these trials that combination therapy as second-line treatment using medications from different classes results in improvement in exercise capacity; evidence on mortality and clinical worsening is inconclusive. In addition, the evidence is lacking on which particular combination of medications is optimal. Clinical input in 2011 uniformly thought that at least some therapy combinations were beneficial. Therefore, combination therapy as second-line treatment may be considered medically necessary when certain conditions are met. Additional trials on combination treatment are underway, including at least one evaluating combination therapy as first-line treatment.

### **Practice Guidelines and Position Statements**

In October 2009, the Health Technology Assessment Program in the U.K. published a systematic review of randomized controlled trials on medications for treatment of pulmonary arterial hypertension. (36) The medications included epoprostenol sodium administered by IV infusion, inhaled iloprost, oral bosentan, oral sitaxsentan and oral sildenafil; all are approved for use in the U.K. The assessment concluded, "All of the five technologies, when added to supportive treatment and used at licensed dose(s), have been shown to be more effective than supportive treatment alone in patients of mixed FC (*functional class*) and other types of PAH. The volume of evidence and patient populations included in the trials varied between the technologies. Current evidence does not allow comparisons between the technologies nor for the use of combinations of the technologies."

In March 2009, the ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension was released. (37) The writing committee consisted of acknowledged experts in the field of PH. This is the first ACCF/AHA clinical expert consensus document on PH. The authors' discussion regarding an evidenced-based treatment algorithm stated that "in general, patients with poor prognostic indexes should be initiated on parenteral therapy, while patients with class II or early II symptoms commonly commence therapy with either endothelin receptor antagonists or PDE-5 inhibitors." The authors also stated that they "caution against widespread treatment of non-PAH PH" until patient benefit has been proven in clinical trials. On the topic of combination therapy, they state ... "Given the availability of medications that target different pathologic processes, combination therapy is an attractive theoretical option in PAH... Multiple randomized controlled trials of combination therapy are currently ongoing, and to adequately study the safety and efficacy of combination therapy, we encourage enrollment into randomized controlled trials. "

In 2009, the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) published guidelines on the diagnosis and treatment of pulmonary hypertension. (38) Regarding treatment of pulmonary arterial hypertension (Group 1), the guidelines state that the results of clinical studies "support the efficacy of the currently approved PAH treatments" However, they note, "the medical and interventional treatments for more advanced cases are still invasive and prone to significant side effects". The guidelines also comment on combination therapy for PAH: "... There are many open questions regarding combination therapy, including the choice of combination agents, the optimal timing [initial combination (in naive patients) or sequential combination (according to the response to the first drug)], when to switch, and when to combine. When combination therapy is considered, patients should be treated within clinical trials or registries whenever possible. Combination therapy of established PAH drugs is recommended for patients not responding adequately to monotherapy, but combination therapy should be instituted by expert centers only. Whether the response to monotherapy is sufficient or not can only be decided on an individual basis. This is judged in an individual patient who, despite monotherapy and optimized background treatment, has an inadequate clinical response."

Updated in 2007, American College of Chest Physicians (ACCP) developed guidelines for the diagnosis and treatment of PAH. (39) The ACCP panel developed a treatment algorithm for PAH. The recommended therapies presented in this algorithm have been evaluated mainly in those with IPAH, or PAH associated with connective tissue disease or anorexigen use. "Extrapolation to other forms of PAH should be made with caution." Country-specific regulatory agency approval status and functional class indications for PAH medications vary. The guideline statements include:

(1) Anticoagulation should be considered for patients with IPAH, and patients with an indwelling catheter for the administration of an intravenous (IV) prostanoid, in the absence of contraindications. Diuretics and oxygen should be added as necessary.

(2) A positive acute vasodilator response is defined as a fall in mean pulmonary artery pressure 10 mm Hg to 40 mm Hg, with an unchanged or increased cardiac output when challenged with inhaled nitric oxide, IV epoprostenol, or IV adenosine.

(3) Consideration should be given to using a PAH-specific medication such as a phosphodiesterase 5 inhibitor, endothelin receptor antagonist, or prostanoid as first-line treatment instead of a CCB in patients with PAH that is not IPAH or PAH associated with anorexigen use, or in those in an advanced functional class (FC) given the exceedingly low long-term response rate to CCB monotherapy in the former and poor prognosis in the latter.

(4) Sustained response to CCB therapy is defined as being in functional class I or II with normal or near-normal hemodynamics after several months of treatment.

(5) The risks and benefits of treatment in early PAH should be considered.

(6) First-line therapy for functional class III includes bosentan, sildenafil, epoprostenol, inhaled iloprost, and treprostinil.

(7) Most experts recommend IV epoprostenol as first-line treatment for unstable patients in functional class IV.

(8) RCTs studying add-on combination treatment regimens are underway.

### **Ongoing Clinical Trials**

A search of the online [ClinicalTrials.gov](http://ClinicalTrials.gov) database in August 2012 identified the following relevant randomized controlled trials that are underway:

NCT01042158: A 36-week trial comparing the combination of tadalafil and ambrisentan to ambrisentan monotherapy and tadalafil monotherapy and eligibility is limited to patients with PAH associated with systemic sclerosis. The study is sponsored by the National Institutes of Health; the expected completion date is May 2013. (40)

NCT01178073: A trial comparing the combination of tadalafil and ambrisentan as first-line therapy to first-line monotherapy with tadalafil or ambrisentan. The study includes patients with PAH (unlike the trial described above; it is not limited to patients with PAH associated with systemic sclerosis). The study will be terminated when a predefined number of events have occurred; the median study duration is expected to be 1.6 years. The study is sponsored by GlaxoSmithKline; the expected date of completion is June 2013. (41)

NCT00303459: A trial comparing the combination of bosentan and sildenafil to sildenafil monotherapy (Compass 2). Patients will be treated with the study drug until the predefined number of morbidity/mortality events is reached. The study is sponsored by Actelion and the expected study completion date is September 2014. (42)

NCT00323297: A trial comparing the combination of bosentan and sildenafil 20 mg three times a day to bosentan and placebo in patients with PAH. The study is sponsored by Pfizer and the expected date of completion is September 2013. (43)

NCT01560624: This double-blind trial is comparing the addition of oral treprostinil or placebo in patients with PAH who have been taking a, or phosphodiesterase inhibitor or endothelin receptor antagonist for 31 to 90 days. The study is sponsored by United Therapeutics and the expected completion date is August 2016. (44)

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## Billing Coding/Physician Documentation Information

Codes	Number	Description
CPT	93503	Insertion and placement of flow-directed catheter (e.g., Swan-Ganz) for monitoring purposes (i.e., as part of dose-ranging study)
ICD-9 Procedure		
ICD-9 Diagnosis	416.0	Primary pulmonary hypertension
	416.8	Secondary pulmonary hypertension
HCPCS	J1325	Injection, epoprostenol, 0.5 mg
	J3285	Injection, treprostinil, 1 mg
	K0455	Infusion pump used for uninterrupted parenteral administration of medication (e.g., epoprostenol or treprostinil)
	K0730	Controlled dose inhalation drug delivery system
	Q4074	Iloprost, inhalation solution, FDA-approved final product, noncompounded, administered through DME, up to 20 mcg
	S0088	Imatinib, 100 mg
	S0090	Sildenafil citrate, 25 mg
	S0155	Sterile dilutant for epoprostenol, 50 ml
	S9347	Home infusion therapy, uninterrupted, long-term, controlled rate intravenous or subcutaneous infusion therapy (e.g., epoprostenol); administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
ICD-10-CM (effective 10/1/14)	I27.0	Primary pulmonary hypertension
	I27.2	Other secondary pulmonary hypertension
	I27.89	Other specified pulmonary heart diseases
ICD-10-PCS (effective 10/1/14)		ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10-PCS code for the initiation of this therapy.
	3E013GC, 3E033GC	Administration, physiological systems and anatomical regions, introduction, percutaneous, other therapeutic substance, code by body part (subcutaneous tissue or peripheral vein)
Type of Service	Drug Therapy	
Place of Service	Inpatient, Home	

### Additional Policy Key Words

Policy Number: 5.01.09

### Related Topics

N/A

### Policy Implementation/Update Information

07/2013 New Policy titled Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension

02/2014 Reviewed – no changes made

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