

MEDICAL POLICY – 5.01.522

Advanced Therapies for Pharmacological Treatment of Pulmonary Arterial Hypertension


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RELATED POLICIES:
5.01.545 Cialis® (tadalafil) for Benign Prostatic Hyperplasia

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Introduction

High blood pressure within the arteries that go to the lungs is known as pulmonary arterial hypertension. With this condition, the small arteries in the lungs become narrow or are completely blocked. Because it's difficult for blood to travel through them, the blood pressure in the lungs increases. The heart has to work harder to push blood through those arteries. This can lead to a weakened heart muscle and eventually heart failure. Treatment depends on the underlying cause of the high blood pressure and the severity of symptoms. There are several different drugs that can be used to manage the condition. Some drugs open narrowed blood vessels, others help relax the blood vessel walls, while yet others act on a specific substance in the walls of blood vessels. This policy describes when specific medications for pulmonary arterial hypertension may be considered medically necessary.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Therapy	Medical Necessity
<p>Treatment of pulmonary arterial hypertension</p>	<p>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:</p> <ul style="list-style-type: none"> • Patients have failed to demonstrate an adequate response to a single medication <p>AND</p> <ul style="list-style-type: none"> • Medications are from different therapeutic classes <p>AND</p> <ul style="list-style-type: none"> • Each medication may be considered medically necessary for the treatment of PAH <p>The following therapies may be considered medically necessary for the treatment of pulmonary arterial hypertension (PAH/ WHO Group 1):</p> <ul style="list-style-type: none"> • Letairis® (ambrisentan) (oral) • Tracleer® (bosentan) (oral) • Flolan® (epoprostenol sodium) (continuous IV infusion) • Ventavis® (iloprostInhalation) (via nebulizer) • Opsumit® (macitentan) (oral) • Adempas® (riociguat) (oral) • Revatio® (sildenafil citrate) (oral) • Adcirca® (tadalafil) (oral) • Remodulin® (treprostinil sodium) (continuous SC infusion, IV infusion), or Tyvaso® (treprostinil sodium) (inhalation via nebulizer), or Orenitram® (oral) • Levitra® (vardenafil) (oral) • Upravi ® (selexipag) (oral)
<p>Treatment of chronic thromboembolic pulmonary hypertension</p>	<p>Adempas® (riociguat) may also be considered medically necessary for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH/ WHO Group 4) in patients who are not surgical candidates, those who have inoperable CTEPH, or those with recurrent or persistent CTEPH after</p>



Therapy	Medical Necessity
	surgical treatment.

Therapy	Investigational
First-line treatment	Combination therapy as first-line treatment is considered investigational.
Other advanced therapies	Use of other advanced therapies for the pharmacologic treatment of pulmonary arterial hypertension (PAH/ WHO Group 1), including but not limited to Gleevec® (imatinib), simvastatin, and atorvastatin, is considered investigational.
Treatment of any other conditions	The use of Adempas® (riociguat) is considered investigational for the treatment of any other conditions or subtypes of PH, except WHO Groups 1 and 4.
Treatment of non-PAH PH conditions	<p>The use of Flolan® (epoprostenol), Remodulin® (treprostinil), Ventavis® (iloprost), Tracleer® (bosentan), Letairis® (ambrisentan), Opsumit® (macitentan), Revatio® (sildenafil), Adcirca® (tadalafil) and Levitra® (vardenafil) is considered investigational for the treatment of non-PAH PH conditions (WHO Groups 2-5), including but not limited to:</p> <ul style="list-style-type: none"> • 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 (sarcoidosis, histiocytosis X and lymphangiomatosis)

Treatment with Flolan® (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.

For combination treatment, riociguat should not be combined with a phosphodiesterase type 5 inhibitor (sildenafil, tadalafil, or vardenafil).

Coding

Code	Description
HCPCS	
J1325	Injection, epoprostenol (Flolan®) , 0.5 mg
J3285	Injection, treprostinil (Remodulin®), 1 mg
J7686	Treprostinil (Tyvaso®), inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, 1.74 mg
K0455	Infusion pump used for uninterrupted parenteral administration of medication (eg, epoprostenol or treprostinil)
Q4074	Iloprost, inhalation solution, FDA-approved final product, noncompounded, administered through DME, up to 20 mcg
S9347	Home infusion therapy, uninterrupted, long-term, controlled rate intravenous or subcutaneous infusion therapy (eg, epoprostenol); administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

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Related Information



Benefit Application

While epoprostenol would generally be considered under medical benefits, use of bosentan, ambrisentan, macitentan, riociguat, iloprost, treprostinil, selexipag, and sildenafil may be considered under pharmacy benefits, as determined by each Member's contract.

Benefit or contract language describing the "least costly alternative" may be applicable to the choice of therapy among epoprostenol, bosentan, ambrisentan, macitentan, riociguat, iloprost, or treprostinil. A generic formulation of epoprostenol is available.

Patients treated with infusion pumps may require a back-up pump. However, the cost of a back-up pump may be included in the home infusion therapy charges or in the HCPCS code. (See [Coding](#) section.)

Sildenafil citrate is available as both Revatio® and Viagra. Benefit or contract language describing the "least costly alternative" may be applicable to this choice. Pricing differences may exist between alternatives. Revatio® is available as a 20-mg tablet. Viagra is available in 25-mg, 50-mg, 100-mg tablets. Generic sildenafil is available.

Tadalafil is available as both Cialis and Adcirca. Benefit or contract language describing the "least costly alternative" may be applicable to this choice. Pricing differences may exist between alternatives. Cialis is available as 2.5-mg, 5-mg, 10-mg, and 20-mg tablets. Adcirca is available as a 20-mg tablet. The recommended initial daily dose of Adcirca is 40 mg once a day (two 20-mg tablets).

Evidence Review

Description

Pulmonary hypertension (PH) refers to the presence of abnormally high pulmonary vascular pressure.

- A subset of patients is 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 analogs, endothelin receptor antagonists, phosphodiesterase type 5 (PDE5) inhibitors, and a soluble guanylate cyclase stimulator are available to treat PAH. Combination advanced therapy also has been proposed.



- Another subset of patients is considered to have chronic thromboembolic pulmonary hypertension (CTEPH), characterized by residual organized thrombi obstructing the pulmonary vasculature. Most patients have a history of acute pulmonary embolism. Standard treatment for CTEPH is pulmonary endarterectomy. The soluble guanylate cyclase stimulator, riociguat, is the only medication currently U.S. Food and Drug Administration (FDA)-approved to treat CTEPH.

There is evidence from multiple randomized controlled trials (RCTs) and meta-analyses of RCTs that monotherapy using prostanoids, endothelin-receptor antagonists, PDE5 inhibitors, or the soluble guanylate cyclase stimulator, riociguat, improves health outcomes in patients with World Health Organization (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 insufficient evidence that simvastatin, atorvastatin, or imatinib are effective for treating patients with PAH, and these medications do not have FDA-approved PAH indications. Thus, simvastatin, atorvastatin, and imatinib are considered investigational.

There is evidence from 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. Additionally, 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 1 evaluating combination therapy as first-line treatment. Riociguat is contraindicated with PDE5 inhibitors.

There is evidence from 1 RCT that riociguat improves health outcomes in patients with CTEPH (WHO Group 4 PH) who are ineligible for pulmonary endarterectomy or have persistent PH after pulmonary endarterectomy. Riociguat is therefore considered medically necessary in these patient groups. Riociguat has not been studied to reduce elevated preoperative pulmonary vascular resistance in patients eligible for pulmonary endarterectomy. There is insufficient evidence for the use of any PAH-specific medication in this setting; clinical input did not support medical necessity of riociguat or PAH-specific medications for this use. Due to lack of evidence and lack of support from clinical vetting, PAH-specific medications and riociguat are considered investigational for this indication.



Background

Pulmonary hypertension (PH)

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.

Classification

Group 1 PAH includes disorders in which with abnormalities of the pulmonary arterial system. The classification of PAH (Group 1) devised in 2003 following the 3rd World Symposium on Pulmonary Arterial

Hypertension, is as follows¹:

- 1. Pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic (IPAH)
 - 1.2. Familial (FPAH)
 - 1.3. Associated with (APAH):
 - 1.3.1. Collagen vascular disease
 - 1.3.2. Congenital systemic-to-pulmonary shunts
 - 1.3.3. Portal hypertension
 - 1.3.4. HIV infection
 - 1.3.5. Drugs and toxins
 - 1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
 - 1.4. Associated with significant venous or capillary involvement:
 - 1.4.1. Pulmonary veno-occlusive disease (PVOD)
 - 1.4.2. Pulmonary capillary hemangiomatosis (PCH)



- 1.5. Persistent pulmonary hypertension of the newborn

In 2013, based on the consensus of an international group of experts at the 5th World Symposium on Pulmonary Hypertension, modifications to the classification of PAH were proposed.² A key difference from the earlier classification, which is still used by the American College of Cardiology Foundation/American Heart Association (ACCF/AHA), is the category of "Group 1 prime," defined as pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH), and "Group 1 prime," defined as persistent pulmonary hypertension of the newborn (PPHN). The ACCF/AHA nomenclature lists these conditions as subcategories of Group 1. Further, the 2013 World Symposium classification moved PH associated with chronic hemolytic anemia to Group 5, Pulmonary hypertension with unclear multifactorial mechanisms. The updated classification of Group 1 PAH, with key changes in bold, is as follows²:

- 1. Pulmonary arterial hypertension (PAH)
 - 1.1. Idiopathic (IPAH)
 - 1.2. Heritable
 - 1.21 BMPR2
 - 1.22 ALK1, ENG, SMAD9, CAV1, KCNK3
 - 1.23 Unknown
 - 1.3. Drug and toxin-induced
 - 1.4. Associated with:
 - 1.4.1. Connective tissue disorder
 - 1.4.2. HIV [human immunodeficiency virus] infection
 - 1.4.3. Portal hypertension
 - 1.4.4. Congenital heart diseases
 - 1.4.5. Schistosomiasis
 - 1' Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
 - 1" Persistent pulmonary hypertension of the newborn (PPHN)



Disease Description

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, 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. Premature death commonly results from right heart failure.

Idiopathic 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 measures:

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 (CCB) therapy. In contrast, patients with a negative vasoreactivity test should be treated with alternative agents; calcium channel blockers (CCBs) have not been 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 (ie, 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.

It is important to emphasize that the approved treatments for PAH (WHO Group 1) have serious adverse effects. With the exception of riociguat, which is also FDA-approved to treat chronic thromboembolic PH (WHO Group 4), none have been shown to be effective in patients with other forms of PH.

Chronic Thromboembolic PH

Classification

In the WHO classification, CTEPH comprises Group 4. The 2003 WHO and current ACCF/AHA classifications divide CTEP into 3 groups: proximal, distal, and nonthrombotic, eg, caused by tumor, parasites, or foreign material.¹ The first 2 groups distinguish proximal CTEPH, which may be treated with pulmonary thromboendarterectomy, from distal CTEPH, which is inaccessible to surgery; however, this distinction can be difficult to make in clinical practice. Additionally, clinical presentation, radiologic findings, and management of CTEPH vary across etiology.² For these reasons, the updated 2009 WHO classification includes only a single CTEPH category with no subcategories.

Disease Description

CTEPH primarily occurs after acute or chronic pulmonary embolism. Progressive pulmonary vascular remodeling (thrombi organization, fibrous stenosis, and microvascular changes)



obstructs pulmonary arteries, leading to PH and right heart failure.^{3,4} Estimated CTEPH incidence among patients who survive an acute pulmonary embolism ranges from 0.6% to 3.8%.^{4,5} However, many patients have no clinical history of pulmonary embolism, and CTEPH is likely underdiagnosed. Additional risk factors include splenectomy, chronic inflammatory states, and hypercoagulability due to the presence of anticardiolipin antibody or elevated factor VIII levels. Diagnosis is made by ventilation-perfusion scan showing large areas of mismatch (segmental or larger). Pulmonary angiography confirms the diagnosis and indicates operability (ie, the extent of proximal and distal disease).⁴

Baseline Assessment of CTEPH

Functional Impairment: Functional classification is determined using both NYHA and WHO classifications previously described. Patients who are ineligible for pulmonary endarterectomy because of distal disease may be candidates for lung transplantation if functional status is adequate (eg, functional class IV decreases the likelihood of receiving a transplant). Patients who are eligible for pulmonary endarterectomy but are considered high risk due to poor functional status (class IV) may have improved surgical outcomes if pretreated with intravenous epoprostenol.⁴

Hemodynamic Derangement

CTEPH is characterized by a mean pulmonary artery pressure greater than 25 mm Hg. European guidelines also require pulmonary capillary wedge pressure of 15 mm Hg or less and PVR greater than 2 Wood units.⁶ In patients with poor hemodynamics (eg, pulmonary artery pressure >50 mm Hg) who are eligible for pulmonary endarterectomy, pretreatment with intravenous epoprostenol is recommended to improve surgical outcomes.⁴

Medical Management of CTEPH

Patients with CTEPH are treated with diuretics and oxygen as needed and with extended or lifelong anticoagulant therapy. Eligible patients undergo pulmonary endarterectomy, which may be curative. Current guidelines recommend medical treatment using PAH therapies when pulmonary endarterectomy is contraindicated (due to significant distal disease or comorbidity) and when pulmonary artery pressures remain elevated after pulmonary endarterectomy (due to residual distal pathology).^{4,7}



The only medication currently FDA-approved for treatment of CTEPH is riociguat. Riociguat is a first-in-class oral soluble guanylate cyclase stimulator. Riociguat stimulates soluble guanylate cyclase both directly and indirectly, by increasing sensitivity of the enzyme to nitric oxide. Thus, riociguat may be effective in conditions in which endogenous nitric oxide (a vasodilator) is depleted.⁸

Rationale

Research Issues

Editorial critiques of the available literature have raised 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 (eg, 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.

Additionally, some authors have questioned the utility of the 6-minute walk distance (6MWD) as an intermediate clinical outcome in therapeutic pulmonary arterial hypertension (PAH) trials.⁹⁻¹¹ It is unclear whether change in 6MWD is associated with clinical outcomes (eg, death, lung transplantation, hospitalization due to worsening PAH, or worsening right heart failure), or whether there is a threshold above and below at which risk for adverse outcomes substantially changes. Two groups attempted to validate the 6MWD and to define a minimal important difference (MID) using different methods. Gabler et al. examined correlations between 6MWD and clinical events in order to establish a threshold that would indicate a significant change in the probability of such events.¹² A significant threshold effect was observed at 41.8 meters. However, the authors noted that “change in 6MWD does not explain a large proportion of the treatment effect, has only modest validity as a surrogate end point for clinical events, and may not be a sufficient surrogate end point.” Mathai and colleagues used anchor- and distribution-based methods and reported MIDs of 38.6 meters and 25.1-38.5 meters, respectively.¹³ The mean of these values was 33 meters, which the authors considered a consensus MID. A 2012 meta-analysis of 22 randomized controlled trials (RCTs) that assessed 6MWD in patients with PAH and reported clinical outcomes found no relationship between changes in 6MWD and clinical outcomes.¹⁴ All 3 of these analyses were based on trials of short duration (eg, 12 weeks) and in treatment-naïve patients; it may be that the utility of the 6MWD is limited to such trials.



PAH Monotherapy using prostanoids, endothelin-receptor antagonists or phosphodiesterase type-5 (PDE5) inhibitors , or a Soluble Guanylate Cyclase Stimulator (Riociguat)

Several meta-analyses that pool the findings of studies evaluating the efficacy of PAH treatments have been published. In 2013, the Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review of the screening, management, and treatments of PAH.¹⁵ McCrory et al. searched the literature through July 2012 using broad inclusion criteria (diagnosis of PAH in patients of any age; RCTs or observational studies; all sample sizes). They identified 27 RCTs (3,587 patients) and 9 observational studies that evaluated the comparative effectiveness and safety of monotherapy or combination therapy for PAH. Data from the observational studies was considered unusable. Twenty-two RCTs compared a single drug (ie, monotherapy) to placebo or standard therapy, defined as supportive treatment (diuretics, oxygen, digoxin, and/or oral anticoagulants) with or without calcium channel blockers (CCBs); 8 studied prostanoids, 8 studied endothelin-receptor antagonists, and 6 studied PDE5 inhibitors. All patients were adults. Median trial duration was 12 weeks (range 4-24). Based on low strength of evidence, prostanoids were associated with lower mortality compared with standard therapy/placebo (odds ratio [OR]: 0.52 [95% confidence interval (CI): 0.29-0.95]). Evidence for endothelin receptor antagonists and PDE5 inhibitors was insufficient to form a conclusion for this outcome. Moderate strength of evidence for each drug class supported an association with improved 6-minute walk distance (6MWD); treatment effects (mean difference in distance walked, intervention – standard therapy/placebo) were 27.9 meters (95% CI: 10.3-45.4) for prostanoids, 39.9 meters (95% CI: 21.4-58.4) for endothelin-receptor inhibitors, and 38.9 meters (95% CI: 22.0-55.9) for PDE5 inhibitors. Endothelin-receptor antagonists and PDE5 inhibitors were associated with lower incidences of hospitalization based on moderate strength of evidence for each drug class; ORs were 0.34 (95% CI: 0.17- 0.69) and 38.9 (95% CI: 22.0- 55.9). Evidence for prostanoids was insufficient to form a conclusion for this outcome. Low strength of evidence for each drug class supported an association with improvements in most hemodynamic measures (pulmonary vascular resistance [PVR], mean pulmonary artery pressure, and cardiac index). However, the clinical significance of the observed treatment effect magnitudes is unclear. Among commonly reported adverse events, high strength of evidence supported a greater incidence of jaw pain and cough with aerosolized prostanoid than with placebo. Moderate strength of evidence supported a greater incidence of headache and flushing with PDE5 inhibitors compared with standard therapy/placebo. The incidence of flushing was greater with aerosolized prostanoids than with standard therapy/placebo, based on moderate strength of evidence.



A 2013 Cochrane review by Liu et al. assessed the efficacy of endothelin receptor antagonists for the treatment of patients with PAH.¹⁶ A literature search through December 2011 identified 12 RCTs (1,471 patients), 11 of which were placebo controlled. The 12th RCT was a head-to-head comparison of bosentan and sildenafil in 26 patients.¹⁷ Seven of 12 trials assessing bosentan comprised 38% of the total patient sample, 2 trials assessing ambrisentan comprised 27%, and 3 trials assessing sitaxsentan comprised 35%. Sitaxsentan is a selective endothelin receptor antagonist (like ambrisentan) that was withdrawn worldwide in 2010 due to fatal hepatotoxicity. Pooled results showed improved outcomes with endothelin-receptor antagonists compared to placebo in 6MWD (mean difference 33.7 meters [95% CI: 24.9-42.5]), proportion of patients with improved WHO or NYHA functional class (OR: 1.6 [95% CI: 1.2-2.1]), proportion of patients with deteriorated functional class (OR: 0.3 [95% CI: 0.2-0.4]), and hemodynamic parameters (mean pulmonary artery pressure, pulmonary vascular resistance, and cardiac index). Based on 22 events in 1,201 patients, the reduction in mortality with endothelin receptor antagonists was not statistically significant (OR: 0.57 [95% CI: 0.26, 1.24]).

In 2009, Galie et al. in Italy published a meta-analysis of RCTs examining approved medications ie, prostanoids, endothelin-receptor antagonists, and PDE5 inhibitors for treating PAH.¹⁸ 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 et al.¹⁸ 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 2009.¹⁹ 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 et al., searched the literature through April 2009 and, like the Ryerson et al. study, included RCTs on adults with PAH.²⁰ However, in this study, both open and blinded trials were included, and eligibility was not limited by type of control group (eg 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% confidence interval 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.

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.²¹ 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.²² 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.²³ 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 58.9%, 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 et al. 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.²⁴ 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 pulmonary hypertension (PH) related to scleroderma to receive either conventional therapy or conventional therapy in addition to epoprostenol therapy.²⁵ 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 et al. reported on a case series of 20 patients with PH secondary to congenital heart disease who had failed to improve clinically with conventional therapy.²⁶ 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.

Remodulin® (treprostinil)

Infused

The FDA approval of Remodulin® (treprostinil) 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.^{27,28} 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 (ie, 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.²⁹ 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.³⁰ 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 (3 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.)

Inhaled

One small uncontrolled series reported treatment of PAH in children. Krishnan et al performed a retrospective cohort study of 29 children (median age 12 years, range 3.2-19) who received inhaled Tyvaso® (treprostinil) for 6 weeks or longer.³¹ Children were patients at one of 2 large pediatric PH centers (Columbia University Medical Center, New York and Children's Hospital, Colorado). Indications for initiation of inhaled treprostinil therapy included symptomatic PAH despite background therapy or as a strategy to transition patients off parenteral prostanoids. Twenty-six patients were on PDE5 inhibitors, 22 were on endothelin-receptor antagonists, 12 were on prostanoids, 18 were on dual therapy, and 5 were on triple therapy. Treprostinil was started at 3 breaths (6 mcg/breath) 4 times daily and titrated to a maximum of 9 breaths 4 times daily in 20 patients. Maximum dose for 9 younger children and patients experiencing side effects was 4-8 breaths 4 times daily. Mean treatment duration was 16 months. Four patients discontinued treatment after 4 months due to progressive pulmonary symptoms, and 1 patient each required dose reduction due to nausea and hypotension. Common adverse effects were cough, sore throat, headache, and nausea. In 13 patients for whom baseline and follow-up data were available, 6MWD improved from 456 ± 72 meters to 498 ± 70 meters. WHO functional class improved in 19 patients and was unchanged in 10. Improvements in hemodynamic parameters (right atrial pressure, pulmonary artery pressure, systemic arterial pressure, PVR, systemic vascular resistance) were observed in 8 patients for whom baseline and follow-up data were available.

Oral

FDA approval of oral Orenitram® (treprostinil) for the treatment of PAH (WHO Group 1) was based in part on 3 short-term RCTs: FREEDOM-C and FREEDOM-C2 in patients receiving background PAH therapy, and FREEDOM-M in previously untreated patients.

FREEDOM-M (N=349 randomized; 228 analyzed) was a 12-week, multicenter, double-blind, placebo-controlled RCT of oral treprostinil monotherapy.³² Eligible patients had PAH; were not currently receiving PDE5-inhibitors, endothelin receptor antagonists, or prostacyclin; and had a minimum 6MWD of 100 meters. Patients were randomized 2:1 to oral treprostinil or matching placebo. Treprostinil was started at 1 mg twice daily and increased as tolerated every 3 days, but based on the FREEDOM-C trial (described next); starting dose was lowered to 0.25 mg twice



daily. The primary end point was change from baseline 6MWD at 12 weeks; the trial was powered to detect a 45-meter between-group difference in 6MWD at 12 weeks. Results were analyzed for only 65% of patients in each group; patients who had access to the 0.25 mg treprostinil dose at the time of randomization and received at least 1 dose of study drug were included (total N=228). For this group, mean age was 39 years, and 71% of patients were from India or China. PAH etiologies were idiopathic or heritable (74%), collagen vascular disease (19%), congenital heart defect (6%), and HIV (1%). Functional status was predominantly WHO class II (33%) and class III (66%). Mean baseline 6MWD was 330 meters. Twenty-six patients (17%) receiving oral treprostinil and 11 patients (14%) receiving placebo discontinued study drug; discontinuations due to adverse events occurred in 6 patients and 2 patients, respectively. Mean dose of treprostinil at week 12 was 3.4 mg twice daily. Missing data were imputed by last observation (or last rank) carried forward. At week 12, there was a statistically significant greater improvement in 6MWD in the treprostinil group compared with placebo (treatment effect, 23 meters [95% CI, 4 to 41]; Hodges-Lehmann rank estimator, $p=0.013$), a finding that was maintained in subgroup analyses. FDA reviewers noted that the robustness of the finding “depends heavily” on the method of analysis used; for example, giving all randomized patients with missing data the lowest score yielded a statistically nonsignificant result ($p=0.92$).³³ There was no statistical between-group difference in time to clinical worsening (defined as in the FREEDOM-C and FREEDOM-C2 trials), a secondary outcome, in any analysis. The most common adverse events in 233 patients randomized to treprostinil were headache (69%), nausea (39%), diarrhea (37%), and jaw pain (25%). Sixteen randomized patients died during the trial, 10 (4%) in the treprostinil group and 6 (5%) in the placebo group. Two deaths within the oral treprostinil group were considered possibly attributable to study drug. FDA reviewers did not note this in their review.³³

Expert opinion on the clinical utility of this drug differs. Although experts agree that oral administration of prostanoid will be a considerable advantage for patients compared with continuous infused or inhaled administration, Feldman et al (2015) in Arizona raised concerns about inadequate dosing, interruptions to dosing, and switching to/from infused or inhaled prostanoids.³⁴ In contrast, Skoro-Sajer et al (2014) in Austria did not share these concerns.³⁵

Ventavis® (iloprost)

FDA approval of Ventavis® (iloprost) 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%).³⁶ 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.

Tracleer® (bosentan)

The FDA approval of Tracleer® (bosentan) 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.³⁷ 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 PAH, 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.³⁸

Letairis® (ambrisentan)

FDA approval of Letairis® (ambrisentan) was based on two 12-week randomized, double-blind, placebo-controlled multicenter studies of 393 patients with PAH.³⁹ 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 PAH, and 32% had PAH 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.⁴⁰ 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.

Opsumit® (macitentan)

The pivotal SERAPHIN trial (2013) assessed the efficacy and safety of Opsumit® (macitentan) to treat PAH.⁴¹ SERAPHIN was an event-driven, double-blind RCT in 742 patients with PAH (55% idiopathic, 31% associated with connective tissue disease, 8% associated with congenital shunt). Both treated (excluding endothelin receptor antagonists) and untreated patients were enrolled. Patients were randomized to placebo or macitentan 3 mg or 10 mg once daily. The primary end point was a composite of morbidity (atrial septostomy, lung transplantation, or worsening of PAH) and all-cause mortality.

Median treatment duration was 2 years 2 months. Primary end point events occurred in 46% of the placebo group, 38% in the 3 mg macitentan group (hazard ratio [HR] vs. placebo, 0.70; 97.5% CI: 0.52 to 0.96; $p=0.01$), and 31% in the macitentan 10 mg group (HR vs. placebo, 0.55; 97.5% CI, 0.39 to 0.76; $p<0.001$). Results were consistent across multiple sensitivity analyses and prespecified subgroups (e.g., use or nonuse of concomitant PAH medication). The change from baseline in 6MWD at 6 months (a secondary outcome) was -9 meters in the placebo group, +7 meters in the 3 mg macitentan group (least squares mean difference vs. placebo, 17 meters; 97.5% CI: -3 to 36; $p=0.01$), and +13 meters in the 10 mg macitentan group (least squares mean difference vs. placebo, 22 meters; 97.5% CI: 3 to 41; $p=0.008$) from a baseline of 360 meters. Improvements in WHO functional class at month 6 in both macitentan groups were statistically significantly greater in both macitentan groups compared with placebo. Serious adverse events and discontinuations due to adverse events occurred with similar frequency in all 3 groups. Adverse events that occurred more commonly in macitentan-treated patients included headache (13% vs. 9%), anemia (11% vs. 3%), and bronchitis (10% vs. 6%). Liver enzyme elevations, which are associated with bosentan (the parent drug of macitentan), occurred in approximately 4% of patients in all 3 groups.



Revatio® (sildenafil citrate)

FDA approval of Revatio® (sildenafil citrate), 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.⁴² 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 et al. published findings from an open-label extension study for which all patients who completed the initial trial were eligible (SUPER-2).⁴³ In the extension study, all patients titrated up to 80 mg sildenafil 3 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, eg, 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 et al. in 2009.⁴⁴ 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.

In 2012, Oudiz et al. reported results from the 52-week, multicenter PHIRST extension study, PHIRST-2.⁴⁵ Of 364 eligible patients (PHIRST completers [n=341] or those who discontinued due to clinical worsening [n=23]), 357 (98%) continued in PHIRST-2. Patients were randomized in a double-blinded fashion to tadalafil 20 mg or 40 mg orally once daily. Sixty-three patients received tadalafil 20 mg in both PHIRST and PHIRST-2, and 69 received tadalafil 40 mg in both studies; all other patients (n=225) were randomized to receive tadalafil 40 mg in PHIRST-2. In the former groups, improvements in 6MWD achieved in PHIRST were maintained in PHIRST-2: In the group that received tadalafil 20 mg in both studies, 6MWD was 406±67 meters at the start and 415±80 meters at week 52 in PHIRST-2 (n=52). In the group that received tadalafil 40 mg in both studies, 6MWD was 413±81 meters at the start and 410±78 meters at week 52 in PHIRST-2 (n=59). In contrast, patients who had received lower tadalafil doses or placebo in PHIRST did not



improve to similar levels after receiving 40 mg for 52 weeks. Headache was the most common adverse event, occurring in 14% and 16% of patients receiving tadalafil 20 mg or 40 mg in both studies, respectively; these incidences were less than those observed in PHIRST (32% and 42%, respectively), suggesting that headache may wane over time.

Levitra® (vardenafil)

Jing et al. published 2 studies from China evaluating Levitra® (vardenafil); 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.⁴⁶ 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 14³ 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 increase in 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 et al in 2011, was conducted at 8 centers in mainland China.⁴⁷ 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%) in the placebo group 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.

Adempas® (riociguat)

The pivotal PATENT-1 trial (2013) assessed the efficacy and safety of Adempas® (riociguat) to treat PAH.⁴⁸ PATENT-1 was a double-blind RCT in 443 adults who had symptomatic PAH (61% idiopathic, 25% associated with connective tissue disease, 8% associated with congenital heart disease). Both treated (excluding phosphodiesterase type 5 inhibitors) and untreated patients were enrolled. Patients were randomized to placebo or riociguat titrated to 0.5 to 2.5 mg 3 times daily. (A second riociguat group capped at 1.5 mg three times daily [63 patients] was excluded from efficacy analyses.) Dose was optimized during the first 8 weeks, and the optimized dose was continued for 4 additional weeks. The primary efficacy outcome was mean change in 6MWD at week 12.

Approximately 90% of patients in both groups completed the trial; 75% of completers in the riociguat group continued the maximum dose to week 12. Mean change in 6MWD was +30 meters in the riociguat group and -6 meters in the placebo group (least-squares mean difference, 36 meters; 95% CI: 20 to 52; $p < 0.001$) from a baseline of 363 meters. Results were consistent across multiple sensitivity analyses and predefined subgroups (eg, use or nonuse of



concomitant PAH medication). Improvements in PVR, Nterminal brain natriuretic peptide, WHO functional class, time to clinical worsening (defined as the first occurrence of death, transplantation, or other indicator of PAH worsening), and Borg dyspnea severity scale (a patient-reported outcome) also were statistically significantly greater in the riociguat group. Adverse events occurred with similar frequency across groups. Adverse events that occurred more commonly in riociguat-treated patients included stomach upset (19% vs. 8%), hypotension (10% vs. 2%), and anemia (8% vs. 2%). Eight riociguat-treated patients (3%) and 9 placebo-treated patients (7%) discontinued study drug due to adverse events. Serious drug-related adverse events that led to riociguat discontinuation included increased hepatic enzyme levels, acute renal failure, and syncope.

Eighty-five percent of patients in the riociguat group enrolled in an extension study. The mean increase in 6MWD in this group was 36 ± 54 meters at week 12 of PATENT-1. At week 12 of the extension study (week 24 of treatment), there was continued improvement reported with a mean increase of 53 ± 62 meters on preliminary analysis. At 1-year follow-up in 324 patients (82%), mean increase in 6MWD from PATENT-1 baseline was 51 ± 74 meters.⁴⁹ WHO functional class improved in 33% of patients, stabilized in 61%, and worsened in 6% compared with PATENT-1 baseline functional class.

Uptravi® (selexipag)

A pivotal Phase 3, randomized, double-blind, placebo-controlled GRIPHON trial (2015) evaluated the efficacy and safety of Uptravi® (selexipag) in 1156 patients with pulmonary arterial hypertension.⁸⁰ Patients were eligible for enrollment if they were not receiving treatment for PAH or if they were receiving a stable dose of an endothelin-receptor antagonist, a phosphodiesterase type 5 inhibitor, or both. The primary endpoint was a composite of death from any cause or a complication related to pulmonary arterial hypertension up to the end of the treatment period. A primary endpoint event occurred in 397 patients, with 27.0% in the selexipag group and 41.6% in the placebo group (hazard ratio 0.60; 99% CI 0.46 – 0.78; $p < 0.001$). Disease progression and hospitalization accounted for 81.9% of the events. The most frequent adverse events leading to discontinuation in the selexipag group (14.3%) were headache (3.3%), diarrhea (2.3%), and nausea (1.7%). No serious adverse events were reported more frequently in the selexipag group than in the placebo group.



Simvastatin

In 2011, Kawut and colleagues published findings of a study evaluating simvastatin and aspirin, alone and together, for treating PAH.⁵⁰ The study used a 2X2 factorial design and was double-blind and placebo-controlled. After enrolling the first 65 patients, the Data Safety and Monitoring Board did an interim analysis. The analysis showed that it was highly unlikely that simvastatin would show improvement in the primary outcome, change in the 6MWD at 6 months, compared to aspirin or placebo and the study was terminated. No other RCTs were identified that studied any statin for treating PAH. This study represents insufficient evidence that simvastatin is an effective treatment for PAH.

Atorvastatin

In 2012, Zeng et al. published a 6-month, randomized, double-blind, placebo-controlled trial of 220 Chinese patients with PAH (83%) or chronic thromboembolic pulmonary hypertension (CTEPH; 6%) in WHO functional class II or III.⁵¹ Patients received atorvastatin 10 mg orally daily or matching placebo in addition to supportive care (diuretics, digoxin, and warfarin). After 6 months, mean difference in 6MWD (atorvastatin – placebo) was 2.5 meters (95% CI: -33-[+]38). There was no statistically significant difference between treatment groups in the proportion of patients who improved or deteriorated in WHO functional class, or in hemodynamic parameters (right atrial pressure, pulmonary artery pressure, cardiac index, PVR, or mixed venous oxygen saturation). There were 9 deaths in the atorvastatin group (8%) and 11 deaths in the placebo group (10%; $p=0.31$). The authors concluded, "Atorvastatin 10 mg daily has no beneficial effect on the natural history of PAH or CTEPH over 6 months."

Section Summary

RCTs and several meta-analyses of RCTs have found that prostanoids, endothelin receptor antagonists, PDE5, and the soluble guanylate cyclase stimulator, riociguat, 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. One terminated trial of simvastatin and 1 double-blind, placebo-controlled trial of atorvastatin indicated lack of efficacy of both drugs for treatment of PAH.



PAH Combination Therapy

RCTs 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 et al. in 2011 included 6 trials.⁵² 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.⁵³ 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 6th article they included; one included Galie et al. (2009),⁴⁴ and the other included Barst et al. 2011.⁴⁸ 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 2013 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review¹⁵ previously described above included 5 RCTs of combination therapies. As in the Fox et al.⁵² and Bai et al.⁵³ meta-analyses, treatments from different classes were combined in the meta-analyses of the AHRQ review, and all treatment combinations were add-on therapies. Evidence was insufficient to form any conclusion about combination therapy in comparison to continuation of monotherapy for the outcomes of mortality or hospitalization. Low strength of evidence supported an association between greater improvement in the 6MWD with combination therapy compared to continued monotherapy (mean difference in distance walked 23.9 meters [95% CI: 8.0-39.9]). Because the magnitude of the treatment effect is less than the commonly accepted MID of 33 meters, the clinical significance of this finding is uncertain.

A 2012 meta-analysis by Zhu et al.⁵⁵ incorporated results from 5^{44,56-59} of the 6 RCTs discussed below; the EARLY trial⁶⁰ evaluating sildenafil add-on therapy to bosentan in mildly symptomatic patients was excluded, and 1 small RCT (N=39) of sildenafil added to bosentan therapy⁶¹ was included. In 3 trials, inhaled prostanoid was added to bosentan or sildenafil, and in 3 trials, a PDE5 inhibitor was added to bosentan or epoprostenol. A total of 735 patients were evaluated for the 6MWD outcome. The pooled treatment effect (weighted mean difference, combination - monotherapy) was 21.6 meters (95% CI: 13.3-29.9), less than the MID described above. For the outcome of clinical worsening (death, hospitalization, symptomatic deterioration, lack of improvement or the need for treatment escalation [such as additional drugs], the development of an interatrial fistula, or lung transplantation), 729 patients were evaluated. The incidence of clinical worsening was lower in the combination therapy group than in the monotherapy group (risk ratio: 0.43 [95% CI: 0.26-0.72]). Results were primarily driven by 2 large trials^{58,59} which together comprised 68% of the patient sample.

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

Three randomized trials evaluated the combination of inhaled iloprost and bosentan on clinical outcomes. In 2006, McLaughlin et al. conducted a randomized double-blind trial of adding iloprost or placebo to bosentan monotherapy in 67 patients with PAH (idiopathic, 55%, associated PAH, 45%).⁵⁶ 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 with the placebo group. Hoepfer et al. reported results from a small ($n=40$), 12-week, nonblinded RCT evaluating the addition of iloprost to bosentan monotherapy in patients with idiopathic PAH (IPAH, WHO Group 1).⁵⁷ 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, VO₂ max (maximum oxygen consumption during exercise), 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 2017, Han et al. published results for an open-label RCT evaluating the combination of bosentan and iloprost in 27 treatment-naïve patients with PAH by comparing to bosentan and iloprost monotherapy.⁸¹ The primary endpoint, 6MWD, was evaluated at 6 weeks and 3 months after initiation of treatment compared with baseline values. The 6MWD significantly improved with combination therapy (95.6 meters and 133.75 meters) compared to both bosentan (1.3 meters and 0.86 meters) and iloprost (-0.67 meters and 10.2 meters) monotherapy groups at week 6 ($p=0.001$) and after 3 months ($p<0.001$). However, due to the small sample size and open-label study design, the study noted that additional studies with large samples and placebo controls were required to further assess the treatment efficacy and tolerability of combination therapy for PAH.

In 2010, McLaughlin et al. evaluated the addition of inhaled treprostinil to oral therapy in a double-blind RCT with 235 patients with PAH.⁵⁸ 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 µg 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 end points 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 (MLWHF) questionnaire; 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. (62) A total of 206 of 235 (88%) patients participated in the extension study. Their mean (SD) 6MWD at baseline was 349 (81) meters. 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 with patients who were not taking inhaled treprostinil.

The 2004 Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH (BREATH-2) trial compared epoprostenol alone with the combination of epoprostenol plus bosentan.⁸² The trial was multicenter, double-blind, and placebo-controlled. It included 33 patients with PAH who were scheduled to begin treatment with epoprostenol. After 2 days of epoprostenol therapy, patients were randomized to add bosentan ($n=22$) or placebo ($n=11$). The double-blind treatment duration was 16 weeks, and the primary efficacy outcome was change in total pulmonary resistance. Five (15%) of 33 patients did not complete the study. At 16 weeks, mean change in total pulmonary resistance did not differ significantly between groups ($-36.3 \text{ dyns}^{-1} \text{cm}^5 \pm 4.3\%$ in the combination treatment group vs $-22.6 \pm 4.3\%$ in the epoprostenol plus placebo group, $p=0.08$). Secondary outcomes also did not differ significantly between groups. For example, the 6MWD increased a median of 68 meters in the combination treatment group and 74 meters in the epoprostenol plus placebo group. Moreover, the modified New York Heart Association functional class improved for 59% of patients in the combination treatment group and 5 patients in the epoprostenol plus placebo group ($p=NS$).

Prostacyclin Analogs and Phosphodiesterase Inhibitors

In the 2010 McLaughlin et al. study, previously discussed, patients on monotherapy were randomized to receive added inhaled treprostinil or placebo; 70 patients were taking sildenafil at baseline.⁽⁵⁸⁾ 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 et al. assessed the effect of adding oral sildenafil to long-term intravenous epoprostenol ($n=267$) with PAH in a 2008 RCT.⁵⁹ 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% CI not reported). Sildenafil also had a beneficial effect on hemodynamic measurements and health-related quality of life.



Prostacyclin Analogs Plus Endothelin Receptor Antagonists and/or Phosphodiesterase Inhibitors

The 2 pivotal trials of oral treprostinil in patients on background PAH therapy, FREEDOM-C and FREEDOM-C2, were similar in design with the exception of the starting dose of oral treprostinil. In FREEDOM-C, starting dose was 1 mg twice daily, which may have reduced tolerability and contributed to a high dropout rate.⁶³ Based on this observation, starting dose in FREEDOM-C2 was decreased to 0.25 mg twice daily.⁶⁴

FREEDOM-C (N=350) and FREEDOM-C2 (N=310) were 16-week, multicenter, double-blind, placebo-controlled RCTs. Eligible patients had symptomatic PAH; were receiving stable doses of approved PDE5 inhibitors and/or endothelin receptor antagonists and could walk a minimum of 100 meters in 6 minutes at baseline (minimum 6MWD). Patients were randomized 1:1 to receive add-on oral treprostinil, administered twice daily at the specified starting dose (1 mg in FREEDOM-C and 0.25 mg in FREEDOM-C2) and increased as tolerated every 3 days, or matching placebo. The primary end point was change from baseline 6MWD at 16 weeks; trials were powered to detect a 35-meter between-group difference in 6MWD at 16 weeks. Secondary end points included time to clinical worsening (eg, death, transplantation, atrial septostomy, hospitalization related to PAH, or initiation of a new PAH therapy).

Mean patient age was 51 years (range, 15-76). PAH etiologies were idiopathic or heritable (66%), collagen vascular disease (29%), congenital heart defect (4%), and HIV (1%). Functional status was predominantly WHO class II (23%) and class III (74%). Mean baseline 6MWD was 345 meters in FREEDOM-C and 330 meters in FREEDOM-C2. In FREEDOM-C, 39 patients (22%) receiving oral treprostinil and 24 patients (14%) receiving placebo discontinued study drug; discontinuations due to adverse events occurred in 25 patients and 8 patients, respectively. No patient in the oral treprostinil group who was subsequently started at a lower dose discontinued treatment due to adverse events. Median treprostinil dose at week 16 was 3 mg twice daily. In FREEDOM-C2, 25 patients (16%) receiving oral treprostinil and 15 patients (10%) receiving placebo discontinued study drug; discontinuations due to adverse events occurred in 18 patients and 5 patients, respectively. Mean maximum dose of treprostinil at week 16 was 3.1 mg twice daily. In both trials, missing data were imputed by last observation (or last rank) carried forward. Neither trial met the primary efficacy end point. Median between-group differences in change from baseline 6MWD at week 16 (oral treprostinil – placebo) were 11 meters and 10 meters in FREEDOM-C and FREEDOM-C2, respectively. No statistically significant between-group differences were observed in subgroup analyses or for any secondary outcome, including time to clinical worsening. In both trials, the most common prostacyclin-related adverse events leading to treprostinil discontinuation were headache (7%), nausea (5%), vomiting (3%), and diarrhea (3%).



Ten patients in FREEDOM-C2 died during the trial, 6 (4%) in the oral treprostinil group and 4 (3%) in the placebo group. Although 3 deaths within the oral treprostinil group were considered possibly attributable to study drug, FDA reviewers considered the deaths due to underlying disease.³³

FDA review documents³³ and the prescribing information for oral treprostinil⁶⁵ describe an open-label extension study for patients who participated in any of the FREEDOM trials, remained on study drug, and completed all scheduled visits (N=824). Patients from treprostinil groups continued dose escalation as tolerated from their final dose during the trial; patients from placebo group initiated treprostinil at 0.25 mg twice daily. PAH etiologies were idiopathic or heritable (70%), collagen vascular disease (24%), congenital heart defect (5%), and HIV (1%). Functional status was predominantly WHO class II (33%) and class III (64%). Mean oral treprostinil dose increased from 3.7 mg twice daily at 6 months to 5.3 mg twice daily at 3 years. Mean and maximal exposure to treprostinil was 2 years and 6 years, respectively. At 1 year, mean change from baseline 6MWD was 26 meters in all patients (monotherapy and add-on therapy). Twenty-three percent of patients discontinued treatment due to adverse events, most commonly PH, headache, and nausea. One-, 2-, and 3-year overall survival estimates (92%, 87%, 82%, respectively) are difficult to interpret in the absence of a control group.

Endothelin-Receptor Antagonists and Phosphodiesterase Inhibitors

An RCT by Galie et al. 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.⁵⁴ 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 idiopathic PAH (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.

In a 2015 prospective, double-blind study by McLaughlin et al.,³³⁴ symptomatic PAH patients received stable sildenafil plus bosentan or placebo.⁸³ The composite primary endpoint was the time to first morbidity/mortality event, defined as all-cause death, hospitalization for PAH worsening or intravenous prostanoid initiation, atrial septostomy, lung transplant, or PAH worsening. The primary endpoint event occurred in 51.4% of patients randomized to placebo and 42.8% to bosentan (hazard ratio 0.83, 97.31% CI 0.58 – 1.19; p=0.2508). The secondary endpoint of change in 6MWD had a mean between-treatment difference at 16 weeks of +21.8 meters (95% CI +5.9 – 37.8 m; p=0.106). Overall, the study showed that combination therapy of



bosentan plus sildenafil was not superior to sildenafil monotherapy in delaying the time to the first morbidity/mortality event, but the authors did note that the complexities of this composite endpoint and extent of missing information due to patients discontinuing the study prematurely are potential contributing factors for this insignificant result. The Galie et al. study on tadalafil, discussed previously,⁴⁴ 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 2011.⁵⁴ 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.

Another double-blind RCT study in 2015 by Galie et al. evaluated 500 patients with PAH who had not previously received treatment to receive initial combination therapy with ambrisentan plus tadalafil, ambrisentan plus placebo, or tadalafil plus placebo.⁸⁴ The primary endpoint was the time to the first event of clinical failure, defined as the first occurrence of a composite of death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response. The endpoint event occurred in 18%, 34%, and 28% of the subjects in these groups, with 31% in the pooled-monotherapy group (hazard ratio 0.50, 95% CI 0.35 – 0.72; $p < 0.001$ for the combination therapy group compared with the pooled-monotherapy group. The study noted that the treatment effect was mainly driven by a lower rate of hospitalization for PAH in the combination therapy group. However, there was actually no significant difference in WHO functional class among study groups at Week 24, despite improvements in other factors.

Tyrosine Kinase Inhibitors and Any of 3 Major Classes of Medications

In 2010, Ghofrani and colleagues published findings of a multisite double-blind Phase II randomized trial evaluating imatinib as an add-on treatment in patients with PAH; the study was conducted at sites in the United States and Europe.⁶⁷ Fifty-nine patients age 18 and older were enrolled; all had been on stable PAH medications for more than 3 months before enrollment but remained symptomatic. Patients were taking a prostacyclin analog, endothelin-receptor antagonist, PDE5, or combinations of these medications. Individuals in WHO functional class II-IV were eligible. Participants were randomized to receive 6 months of treatment with imatinib or placebo. Thirty-eight of 59 (64%) completed the study; 2 patients in each group died during the follow-up period. Analysis was intention to treat. In the treatment group, an initial dose of 200 mg oral imatinib was given for 2 weeks; if tolerated, the dose was increased to 400 mg. The primary efficacy outcome was change in the 6MWD. At 6 months, mean change in the 6MWD



was an increase in 22 meters in the imatinib group and a decrease of 1 meter in the placebo group; this difference was not statistically significant, $p=0.21$. Findings were similar regardless of the method used to impute missing data.

In 2013, Hoepfer et al. published a 6-month, international, randomized, placebo-controlled trial of add-on imatinib 400 mg orally once daily (reduced to 200 mg if not tolerated) in 202 patients with advanced PAH who were receiving at least 2 PAH therapies.⁶⁸ Most patients (approximately 40% in each group) were receiving triple therapy with an endothelin-receptor antagonist, a PDE5 inhibitor, and a prostanoid. The trial was completed by 67% of imatinib-treated patients and 82% of placebo-treated patients; most discontinuations were due to adverse events in both groups (26% in the atorvastatin group, 7% in the placebo group). The mean between-group difference in 6MWD (imatinib-placebo) was 32 meters (95% CI: 12-52), a finding that was robust to multiple modes of imputing missing data. Mortality, functional class, and time to clinical worsening (death, overnight hospitalization for worsening PAH, worsening of WHO functional class by at least 1 level, or a 15% or greater decrease from baseline 6MWD) did not differ between treatment groups. In a subset of 150 patients (approximately 70 imatinib-treated and 80 placebo-treated patients), statistically significant improvements in hemodynamic parameters (PVR, cardiac output, mean pulmonary artery pressure, and right atrial pressure) were observed with imatinib compared to placebo. Of 150 patients who completed the trial, 144 (66 imatinib-treated and 78 placebo-treated patients) entered an extension study of open-label imatinib. Among patients who received 48 weeks of imatinib therapy, mean increase in 6MWD from baseline was 45 ± 46 meters; among placebo-treated patients who received imatinib in the extension study (24 weeks of imatinib therapy), mean increase in 6MWD from baseline was 19 ± 72 meters ($p=0.98$). Serious adverse events occurred in 44% of the imatinib group and 30% of the placebo group; the most common serious adverse events in the imatinib group trial were anemia, dyspnea, peripheral edema, and presyncope. Subdural hematoma occurred in 8 patients co-treated with imatinib and anticoagulation and in no patients treated with placebo. Given the risk-benefit profile observed in the trial, the authors conclude that “the off-label use of imatinib for this indication is strongly discouraged.”

Section Summary

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 RCTs 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. Randomized trials of imatinib add-on therapy indicated no additional improvement with imatinib in most outcomes measured, and potential harm (subdural hematoma).

CTEPH Monotherapy

Riociguat

The pivotal CHEST-1 trial (2013) assessed the efficacy and safety of riociguat to treat CTEPH.⁶⁹ CHEST-1 was a double-blind RCT in 261 adults who had inoperable CTEPH (72%) or persistent PH after pulmonary endarterectomy (28%). Patients receiving PAH medications were excluded. Patients were randomized to placebo or riociguat titrated to 0.5 to 2.5 mg three times daily. Dose was optimized during the first 8 weeks, and the optimized dose was continued for 8 additional weeks. The primary efficacy outcome was change in 6MWD at 16 weeks.

Approximately 93% of patients in each group completed the trial; 77% of completers in the riociguat group continued the maximum dose to week 16. Mean change in 6MWD was +39 meters in the riociguat group, and -6 meters in the placebo group (least-squares mean difference, 46 meters; 95% CI: 25 to 67; $p < 0.001$) from a baseline of 347 meters. Results were consistent across multiple sensitivity analyses and predefined subgroups (eg, baseline WHO functional class). Improvements in PVR, N-terminal brain natriuretic peptide, and WHO functional class also were statistically significantly greater in the riociguat group. Adverse events occurred in 92% of the riociguat group and 86% of the placebo group. Adverse events that occurred more commonly in the riociguat group included headache (25% vs. 14%), dizziness (23% vs. 12%), stomach upset (18% vs. 8%), vomiting (10% vs. 3%), diarrhea (10% vs. 5%), and hypotension (9% vs. 3%). The most common serious adverse events were right ventricular failure (3% in each group), syncope (2% riociguat vs 3% placebo), and hemoptysis (2% riociguat). One patient died due to acute renal failure attributed to riociguat.

Seventy-five percent of patients in the riociguat group enrolled in an extension study; mean increase in 6MWD in this group was 51 ± 62 meters at week 16 of CHEST-1 and 63 ± 64 meters in preliminary analysis at week 12 of the extension study (week 28 of treatment).

Additional data on secondary outcomes from CHEST-1 were published by Kim et al in 2017⁸⁵ Study findings generally favored the riociguat group. At week 16, compared with baseline, PVR significantly decreased in the riociguat group (-29%) compared with the placebo group (+3%).



There were also significantly improved outcomes in the riociguat group vs placebo for other hemodynamic outcomes (eg, systemic vascular resistance, mean pulmonary artery pressure, diastolic pulmonary artery pressure, cardiac output, mixed venous oxygen saturation, mean arterial pressure, diastolic pressure gradient; $p < 0.001$ for each).

CTEPH Perioperative Therapy

For patients with CTEPH who are eligible for pulmonary endarterectomy, preoperative elevation of PVR (> 1100 Wood units) can increase operative mortality rates to 6% to 10%.⁽⁷⁰⁾ Several studies have investigated the use of PAH-specific treatments to reduce elevated PVR preoperatively in patients with CTEPH who are candidates for pulmonary endarterectomy.

Bosentan

In 2010, Reesink et al. reported results of a single-blind RCT in 26 patients with CTEPH who were eligible for pulmonary endarterectomy.⁷¹ Mean baseline total pulmonary resistance was approximately 1000 Wood units. Fourteen patients received bosentan for 16 weeks before surgery; 1 patient developed liver enzyme elevations to 6 times the upper limit of normal and was excluded from efficacy analyses. Eleven patients in the bosentan group and 10 patients in the no-bosentan group underwent pulmonary endarterectomy. Mortality rates within 30 days after surgery were 9% and 30%, respectively.

Epoprostenol

Nagaya et al. (2003) retrospectively examined the effect of preoperative intravenous prostacyclin analog (epoprostenol).⁷⁰ Of 33 consecutive patients with CTEPH who underwent pulmonary endarterectomy, 12 patients with preoperative PVR greater than 1200 Wood units received preoperative epoprostenol for a mean of 6 ± 2 weeks. Statistically significant reductions in PVR before surgery and further reductions after surgery led to a statistically nonsignificant difference between groups 1 month after surgery (mean PVR approximately 300 Wood units in both groups). The only patient who died within 30 days after surgery was in the epoprostenol group for an overall mortality rate of 3.0% (8.3% mortality rate in the epoprostenol group; 0% in the comparator group).

In a similar study, Bresser et al. (2004) retrospectively reviewed 9 patients who had received IV epoprostenol for a median of 4 months (range, 2-26) before pulmonary endarterectomy.⁷²



Median baseline total pulmonary resistance was 1432 Wood units, and median baseline PVR was 1031 Wood units. (Baseline PVR could not be calculated in 1 patient.) Preoperatively, median total PVR decreased to 1000 Wood units, and median PVR decreased to 760 Wood units. Median total pulmonary resistance on postoperative day 1 or 2 was 350 Wood units.

Iloprost

In 2003, Kramm et al. reported on the effect of inhaled iloprost in the perioperative period.⁷³ Ten patients with mean PVR of 972 Woods units received inhaled iloprost at 3 time points: immediately before surgery, upon admission to the intensive care unit after surgery, and at 12 or more hours after surgery. Preoperative inhalation did not affect PVR. After surgery, PVR decreased 10% and 22% after each postoperative dose compared with placebo (saline) inhalation at the same time points; however, all postoperative measurements (pre- and posttreatment) were less than 360 Wood units. One patient died 17 days after surgery due to persistent pulmonary hypertension (10% mortality rate).

Riociguat

There are no trials evaluating riociguat for preoperative therapy. Because of the different mechanism of action for the different drugs, results from the studies previously described cannot be extrapolated to riociguat.

Summary of Evidence

There is evidence from multiple randomized controlled trials (RCTs) and meta-analyses of RCTs that monotherapy using prostanoids, endothelin-receptor antagonists, phosphodiesterase type 5 (PDE5) inhibitors, or the soluble guanylate cyclase stimulator, riociguat, improves health outcomes in patients with World Health Organization (WHO) Group 1 PAH. Thus, U.S. Food and Drug Administration (FDA)-approved medications in these classes may be considered medically necessary for the treatment of patients with pulmonary arterial hypertension (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 insufficient evidence that simvastatin, atorvastatin, or imatinib are effective for treating patients with PAH, and these medications do not have FDA-approved PAH indications. Thus, simvastatin, atorvastatin, and imatinib are considered investigational.



There is evidence from 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. Additionally, 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 1 evaluating combination therapy as first-line treatment. Riociguat is contraindicated with PDE5 inhibitors.

There is evidence from 1 RCT that riociguat improves health outcomes in patients with chronic thromboembolic pulmonary hypertension (CTEPH; WHO Group 4 PH) who are ineligible for pulmonary endarterectomy or have persistent pulmonary hypertension (PH) after pulmonary endarterectomy. Riociguat is therefore considered medically necessary in these patient groups. Riociguat has not been studied to reduce elevated preoperative pulmonary vascular resistance in patients eligible for pulmonary endarterectomy. There is insufficient evidence for the use of any PAH-specific medication in this setting; clinical input did not support medical necessity of riociguat or PAH-specific medications for this use. Due to lack of evidence and lack of support from clinical vetting, PAH-specific medications and riociguat are considered investigational for this indication.

Ongoing and Unpublished Clinical Trials

A search of the online [ClinicalTrials.gov](https://clinicaltrials.gov) database identified the following relevant RCTs that are underway:

Pulmonary Arterial Hypertension

- NCT01178073: A trial comparing the combination of tadalafil and ambrisentan as first-line therapy to first-line monotherapy with tadalafil or ambrisentan in patients with PAH. The study will be terminated when a predefined number of events has occurred; the median study duration is expected to be 2.0 years. The trial is sponsored by GlaxoSmithKline, and the expected completion date is August 2014; results have not been posted.
- NCT01558466: In this randomized, placebo-controlled, double-blind trial, inhaled nitric oxide will be combined with sildenafil or placebo to treat 200 newborns with persistent pulmonary hypertension and or hypoxemic respiratory failure. Effect on oxygenation, duration of



mechanical ventilation, and rebound hypoxic episodes will be observed. The trial is sponsored by Hamad Medical Corporation, and the expected completion date is June 2015.

- NCT01560624: This double-blind trial (FREEDOM-EV) compares the addition of oral treprostinil or placebo in patients with PAH who have been taking a phosphodiesterase inhibitor or endothelin receptor antagonist for 31 to 90 days. The trial is sponsored by United Therapeutics, and the expected completion date is August 2016.
- NCT02060487: Pfizer is sponsoring this phase 4, randomized, double-blind trial (AFFILIATE) to compare the effects of 3 doses of sildenafil (5 mg, 20 mg, or 80 mg 3 times daily) on overall survival in patients with PAH, functional class II-IV, and baseline 6MWD of 50 meters or more. Estimated enrollment is 429, and expected completion date is June 2022.
- NCT01824290: Eli Lilly is sponsoring this phase 3, 24-week, randomized, double-blind, placebo-controlled trial to assess the efficacy of tadalafil in pediatric patients (age, 6 months-18 years) with PAH who are maintained on stable endothelin receptor antagonist therapy (WHO functional class II-III). The primary outcome measure is change in 6MWD; secondary outcomes include time to clinical worsening. Survival outcomes are not addressed. Estimated enrollment is 134, and expected completion date is December 2022.
- NCT01908699: Lung Biotechnology, Inc. is sponsoring this phase 3, U.S., multicenter, randomized, double-blind, placebo-controlled trial (BEAT) of oral beraprost added to inhaled treprostinil in adults with PAH, WHO functional class III-IV, and baseline 6MWD of 100 meters or more. The primary outcome measure is time to clinical worsening. Estimated enrollment is 240, and expected completion date is November 2016.

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- NCT01884675: This phase 3, placebo-controlled, double-blind RCT assesses the endothelin receptor antagonist, ambrisentan, in 160 patients with inoperable CTEPH. Treatment duration is 16 weeks. The trial is sponsored by GlaxoSmithKline, and the expected completion date is September 2015.
- NCT01416636: This phase 3, double-blind RCT compares low and high doses of subcutaneous treprostinil in patients with severe, inoperable CTEPH. Treatment duration is 24 weeks. The trial is sponsored by SciPharm SàRL, and the expected completion date is December 2014.



CTEPH

- NCT01884675: This Phase III, placebo-controlled, double-blind RCT assesses the endothelin receptor antagonist, ambrisentan, in 160 patients with inoperable CTEPH. Treatment duration is 16 weeks. The trial is sponsored by GlaxoSmithKline, and the expected completion date is June 2015.
- NCT01416636: This Phase III, double-blind RCT compares low and high doses of subcutaneous treprostinil in patients with severe, inoperable CTEPH. Treatment duration is 24 weeks. The trial is sponsored by SciPharm SàRL, and the expected completion date is December 2014.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

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.

2011

In response to requests, input was received through 4 academic medical centers while this policy was under review in 2011. 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 1 medication to another). The other 2 academic medical centers had mixed input; both thought there were situations in which combination therapy is medically necessary.

2014

In response to requests, input was received through 4 academic medical centers (5 reviewers) and 1 professional pharmacy society while this policy was under review in 2014. The input focused on:



- The use of riociguat and PAH-specific medications to reduce PVR preoperatively in patients with CTEPH who are candidates for pulmonary endarterectomy: There was consensus among reviewers that riociguat is investigational in this setting, and there also was consensus that PAH specific medications are investigational in this setting.
- The use of riociguat in patients with CTEPH who are candidates for pulmonary endarterectomy but prefer medical treatment: Results of vetting were mixed on this question.

2016

A literature search was conducted between November 1, 2015, and November 30, 2016. Research did not yield additional evidence to prompt a change to the existing policy criteria. References section was updated with four additional articles.

2017

A literature search was conducted between November 30, 2016, and October 31, 2017. References section was updated with six additional articles. Oral Uptravi® (selexipag) was added to the medically necessary policy statement.

Practice Guidelines and Position Statements

Pulmonary Arterial Hypertension

In 2013, the 5th World Symposium on Pulmonary Hypertension was held in France, and an updated evidence- and consensus-based treatment algorithm was produced.⁷⁴ Initial therapy with advanced pharmacologic treatments approved for PAH is recommended for WHO functional class II-IV PAH. (Level of recommendation: I [evidence and/or agreement that treatment is beneficial] to IIa [evidence is conflicting and/or opinions diverge, but the weight of evidence/opinion favors usefulness]), depending on drug; level of evidence: A [multiple RCTs or meta-analyses] to C [consensus opinion, small studies, retrospective studies, registries], depending on drug.) Initial combination therapy received a level IIb recommendation (evidence is conflicting and/or opinions diverge, and usefulness is less well-established) based on level C



evidence. For patients with an inadequate clinical response to initial treatment, combination therapy is recommended (level I recommendation based on level A evidence).

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 PAH.⁷⁵ 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.⁴ 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.⁶ 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.⁵³ 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.



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The 2009 ACCF/AHA Expert Consensus Document on Pulmonary Hypertension recommended pulmonary endarterectomy for eligible patients with CTEPH.⁽⁴⁾ The panel noted that pharmacotherapy with PAH-specific medications may benefit CTEPH patients who are ineligible for pulmonary endarterectomy due to significant distal disease or comorbidity; patients who have persistent pulmonary hypertension due to residual distal disease after pulmonary endarterectomy; and patients eligible for pulmonary endarterectomy who are considered high-risk due to poor functional status or hemodynamics and may benefit from presurgical treatment with intravenous epoprostenol. The panel recommended that PAH-specific medications be used for CTEPH patients only when “appropriate secondary preventive measures, including anticoagulation, have been instituted” and “the patient’s symptoms suggest that PAH-specific therapy may yield clinical benefit.”

The 2009 European Society of Cardiology/European Respiratory Society (ESC/ERS) guideline also recommends pulmonary endarterectomy for patients with CTEPH.⁶ Like the ACCF/AHA consensus document, PAH-specific drug therapy is recommended for “selected CTEPH patients such as patients not candidates for surgery or patients with residual pulmonary hypertension after pulmonary endarterectomy.”

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Regulatory Status

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



Table 1: Advanced Treatments of PAH and Their Regulatory Status

Drug Brand Name Manufacturer FDA Approval Date	Route(s) of Administration Dose range	FDA Approved Indications
Prostacyclin Analogues		
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	Treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
treprostinil sodium (REMODULIN®) United Therapeutics Corp. FDA approved 2002	Continuous subcutaneous (SC) infusion IV infusion (if SC infusion not tolerated) 0.625 to 1.25 ng/kg/min	Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms. 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 (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms .
(ORENITRAM®) United Therapeutics Corp. FDA approved 2013	Oral Maximum dose as tolerated: 3.4-21 mg twice daily ³	Treatment of PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).
iloprost (VENTAVIS®) Actelion, Ltd.	Inhalation via nebulizer; specific to one pulmonary drug delivery system 2.5 to 5 mcg, 6-9 times/day	Treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of



Drug Brand Name Manufacturer FDA Approval Date	Route(s) of Administration Dose range	FDA Approved Indications
FDA approved 2004		deterioration. Studies establishing effectiveness predominately included patients with NYHA Functional Class III-IV symptoms .
beraprost NOT APPROVED IN U.S. & EU Failed reviews Approved in Japan for treatment of PAH	Oral	No FDA-approved indications for PAH.
Prostacyclin receptor agonists		
Selexipag (UPTRAVI®) Actelion, Ltd. FDA approved 2015	Oral Starting dose 200 mcg twice daily. Increase by 200 mcg twice weekly to maximum tolerated dose up to 1600 mcg twice daily	Treatment of PAH (WHO Group 1) to improve delay disease progression and reduce risk of hospitalization for PAH. Study establishing effectiveness had long-term follow-up and included patients with WHO functional class II-III symptoms.
Endothelin Receptor Antagonists		
bosentan (TRACLEER®) Actelion, Ltd. FDA approved 2001	Oral 62.5 to 125 mg 2 times/day	Treatment of PAH (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness predominantly included patients with NYHA Functional Class II-IV symptoms .
ambrisentan (LETAIRIS®) Gilead Sciences, Inc. FDA approved 2007	Oral 5-10 mg/day	Treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness predominantly included patients with NYHA Functional Class II-III symptoms
macitentan (OPSUMIT®)	Oral 10 mg/day	Treatment of PAH (WHO Group 1) to delay disease progression (defined as death, initiation of IV or SC prostenoids,



Drug Brand Name Manufacturer FDA Approval Date	Route(s) of Administration Dose range	FDA Approved Indications
Actelion Pharmaceuticals FDA approved 2013		or clinical worsening of PAH [decreased 6-minute walk distance, worsened PAH symptoms, and need for additional PAH treatment]). Macitentan also reduced hospitalization for PAH.
Phosphodiesterase (PDE5) Inhibitors		
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 (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness predominately included patients with NYHA Functional Class II-III symptoms.
vardenafil (LEVITRA®) FDA approved (but not for PAH)	Oral	No FDA-approved indications for PAH. One randomized trial outside of U.S.
Soluble Guanylate Cyclase Stimulators		
riociguat (ADEMPAS®) Bayer HealthCare Pharmaceuticals FDA approved 2013	Oral 0.5-2.5 mg 3 times/day	Treatment of PAH (WHO Group 1) to improve exercise capacity and WHO functional class, and to delay clinical worsening. The pivotal study establishing efficacy and safety for this condition predominantly included patients with NYHA Functional Class II-III symptoms. Treatment of persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional



Drug Brand Name Manufacturer FDA Approval Date	Route(s) of Administration Dose range	FDA Approved Indications
		class.
Tyrosine kinase inhibitors		
imatinib (GLEEVEC®) FDA approved (but not for PAH)	Oral	No FDA-approved indications for PAH. Two randomized trials as add-on medication.
Statins		
Simvastatin FDA approved (but not for PAH)	Oral	No FDA-approved indications for PAH. One randomized trial with and without aspirin showed no effect on exercise ability.
Atorvastatin FDA approved (but not for PAH)	Oral	No FDA-approved indications for PAH. One randomized trial showed no clinical benefit compared with placebo.

CTEPH: chronic thromboembolic pulmonary hypertension; FDA: U.S. Food and Drug Administration; PAH: pulmonary arterial hypertension; SC: subcutaneous; NYHA: New York Heart Association; WHO: World Health Organization.

^aMean dose in a controlled clinical trial at 12 wk was 3.4 mg twice daily. Maximum doses studied were 12 mg twice daily in a 12-wk blinded study and 21 mg twice daily in an open-label long-term study

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History

Date	Comments
06/25/98	Add to Prescription Drug Section - New Policy
12/21/00	Replace Policy - Policy updated; policy statement revised to include new FDA approved indication for treatment of secondary PH.
03/11/03	Replace Policy - Policy reviewed and updated with literature review; discussion of new drugs treprostinil and bosentan added. Policy retitled to reflect discussion of new drugs.
05/11/04	Replace Policy - Policy reviewed and updated; references added; no change in policy statement.
06/14/05	Replace Policy - Policy updated with policy statement revised to state that iloprost may be considered medically necessary reflecting FDA approval; references and codes added.
02/06/06	Codes updated - No other changes.
06/16/06	Update Scope and Disclaimer - No other changes.
08/08/06	Replace Policy - Policy updated and policy revised to include sildenafil as a consideration for medically necessary treatment reflecting FDA approval; references added.
08/21/06	Codes Updated - No other changes
03/10/09	New PR Policy - New PR policy, replaces BC.5.01.09. Policy statement updated to include Investigational statement relating to combination therapy and medically necessary statement regarding the prevention and/or healing of ischemic digital ulcers in patients with severe Raynaud's phenomenon. References added. Reviewed and recommended by P&T in November 2008.
10/12/10	Replace Policy - Reviewed and recommended by OAP in August 2010 and P&T in September 2010. Policy revised with literature search; references with 2009 references renumbered. The policy statement has been updated: Tyvaso has been added to treprostinil policy statement; tadalafil (ADCIRCA) added as medically necessary; and a medically necessary statement has been added indicating all listed therapies for the prevention and/or healing of ischemic digital ulcers in patients with severe Raynaud's phenomenon secondary to scleroderma/systemic sclerosis and who are refractory to optimized dosing of at least two conventional pharmacotherapies. No other change in policy statements.
11/10/11	Replace Policy – Policy updated with literature review; references 45 and 46 added. No change in policy statement. Reviewed by P&T September 27, 2011.
11/13/12	Replace policy. Policy updated with literature search through July 2012. Policy title changed to: "Advanced Therapies for Pharmacological Treatment of Pulmonary Arterial



Date	Comments
	Hypertension." Policy statement added that "use of other advanced therapies for the treatment of pulmonary arterial hypertension (PAH/ WHO Group 1), including but not limited to imatinib and simvastatin, is considered investigational." Policy statement on combination therapy reformatted as bulleted list; statement that each medication needs to be considered medically necessary was added. Policy now aligns with BCBSA 5.01.09, with an additional medically necessary policy statement allowing addressed therapies for the prevention and/or healing of ischemic digital ulcers in patients with severe Raynaud's phenomenon secondary to scleroderma and who are refractory to optimized dosing. Rationale and References updated to support policy statements. HCPCS code S0088 and ICD-10 codes added.
08/15/13	Update Related Policies. Add 5.01.545.
12/09/13	Replace policy. Policy completely rewritten to mirror BCBCSA policy 5.01.09; adding macitentan (OPSUMIT [®]) oral (PAH/ WHO Group 1) and riociguat (ADEMPAS [®]) (PAH/ WHO Group 1 and CTEPH/ WHO Group 4) to the list of drugs considered medically necessary. Description and Rationale sections updated to provide supporting information to updates in Policy. References 54-56 added. CPT code 93503 and HCPCS codes K0730, S0088, K0090, and S0155 removed; these do not apply specifically to the policy and are purely informational.
12/17/14	Annual Review. Policy updated with input from clinical reviewers; references 2, 14, and 42 updated. ICD-10 PCS codes removed; not utilized in policy adjudication.
01/05/15	Update Related Policies. Add 5.01.545.
05/12/15	Annual Review. Policy updated with literature review through February 2, 2015; references 11, 32-35, 49, 63-66, and 74 added; reference 36 updated. Oral treprostinil (Orenitram [®]) added to medically necessary policy statement.
01/01/17	Annual Review, approved December 13, 2016. Research did not yield additional evidence to prompt a change to the existing policy criteria. References section was updated with four additional articles.
12/01/17	Annual Review, approved November 21, 2017. References section was updated with six additional articles (references 80 - 85). Oral selexipag (Uptravi [®]) added to medically necessary policy statement. Added HCPCS code J7686. *This policy varies slightly from the BCBSA reference policy.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.



Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.



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- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
 - Qualified sign language interpreters
 - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
 - Qualified interpreters
 - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at <https://ocrportal.hhs.gov/ocr/portal/lobby.jsf>, or by mail or phone at: U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at <http://www.hhs.gov/ocr/office/file/index.html>.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማርኛ (Amharic):

ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀዳሾች ሊኖሩ ይችላሉ። የጤና ሽፋንዎን ለመጠበቅና በአስፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና የለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መሰታ አለዎት። በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):

يحتوي هذا الإشعار على معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تزيد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو المساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ 800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

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Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

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Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

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Tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsawb ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam hnuv ntawm Premera Blue Cross. Tej zaum muaj cov hnuv tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

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Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyonyo wenna coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyto wenna tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

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본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하의 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):

ແຈງການນີ້ມີຂໍ້ມູນສໍາຄັນ. ແຈງການນີ້ອາດຈະມີຂໍ້ມູນສໍາຄັນກ່ຽວກັບຄໍາຮ້ອງສະໝັກ ຫຼື ຄວາມຄົມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີ່ສໍາຄັນໃນແຈງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດໍາເນີນການຕາມກຳນົດ ເວລາສະເພາະເພື່ອຮັກສາຄວາມຄົມຄອງປະກັນສະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເວັ້ນເວີ້ ຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄດ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໃບທາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):

សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរៀបចំរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ជាក់សមត្ថភាព ដល់កិច្ចការផ្ទៃក្នុងដូចជា ធានា ដើម្បីនឹងរក្សាទុកការធានារ៉ាប់រងអនាគតរបស់អ្នក ឬប្រាក់ជំនួយចេញថ្លៃ។ អ្នកមានសិទ្ធិទទួលបានព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):

ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਟਿਸ ਨਵ ਖਾਸ ਤਾਰੀਖਾਂ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀਂ ਜਸਰਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾਂ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ ਤੋਂ ਪਹਿਲਾਂ ਢੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫਤ ਵਿੱਚ ਤੋਂ ਅਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):

این اعلامیه حاوی اطلاعات مهم میباشد. این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید. شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید. شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کلیران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):

To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):

Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastră de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența provizorie la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):

Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):

Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'matalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):

Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganiitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):

ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับกาการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):

Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страховального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):

Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).