Medical Policy

MP 5.01.509
Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

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

- epoprostenol sodium (e.g., Flolan®) continuous intravenous infusion;
- treprostinil sodium (Remodulin®) continuous SC infusion, intravenous infusion; (Tyvaso®) inhalation via nebulizer; or (Orenitram®) oral;
- iloprost (Ventavis®) inhalation via nebulizer;
- bosentan (Tracleer®) oral;
- ambrisentan (Letairis®) oral;
- sildenafil citrate (e.g., Revatio®) oral;
- tadalafil (Adcirca®) oral;
- vardenafil (Lевitra®) oral;
- riociguat (Adempas®) oral;
- macitentan (Opsumit®) oral.
- selexipag (Uptravi®)

Combination therapy with Letairis (ambrisentan) and Adcirca (Tadalafil) for the treatment of pulmonary arterial hypertension (PAH/WHO Group 1) may be considered medically necessary.

Combination therapy (other than Letairis and Adcirca) for the treatment of pulmonary arterial hypertension (PAH/WHO Group 1) may be considered medically necessary when all of the following conditions are met (see Policy Guidelines section):

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

Combination therapy as first-line treatment is considered investigational for any other combination...
Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

therapy besides Letairis (ambrisentan) and Adcirca (Tadalafil).

Use of other advanced therapies for the pharmacologic treatment of pulmonary arterial hypertension (PAH/WHO group 1) that are not approved by the U.S. Food and Drug Administration for this indication, including but not limited to imatinib, simvastatin, and atorvastatin, is considered investigational.

PULMONARY HYPERTENSION

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

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

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

The use of riociguat (Adempas®) for the treatment of chronic thromboembolic pulmonary hypertension (CTEPH/WHO Group 4) may be considered medically necessary in the following conditions:

- Persistent pulmonary hypertension after surgical thrombectomy; or
- Inoperable CTEPH.

The use of riociguat or PAH-specific medications to reduce pulmonary vascular resistance before surgery in patients with CTEPH who are considered candidates for pulmonary endarterectomy is considered investigational.

The use of riociguat is considered investigational for the treatment of WHO Groups 2, 3, and 5 pulmonary hypertension, including but not limited to:

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

POLICY GUIDELINES

Treatment with epoprostenol requires 3 steps: initial dose-ranging, catheter insertion and portable pump attachment, and catheter and pump maintenance.

- An initial dose-ranging study is typically performed as an inpatient. The pulmonary capillary wedge pressure is monitored, and the drug infusion rate 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. Because rebound pulmonary hypertension may recur if the drug is abruptly withdrawn, the drug labeling advises that all patients have access to a backup infusion pump and intravenous infusion set.
- For ongoing maintenance of portable infusion pump and treatment of complications related to the pump, complications include catheter thrombosis, sepsis, and pump malfunction. In 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. Oral treprostinil should only be prescribed by a physician with expertise in treating pulmonary arterial hypertension, including administration of infused prostanoids. For combination treatment, riociguat should not be combined with a phosphodiesterase type 5 inhibitor (sildenafil, tadalafil, vardenafil).

**BENEFIT APPLICATION**

**BLUECARD/NATIONAL ACCOUNT ISSUES**

While epoprostenol would generally be considered under medical benefits, the use of bosentan, ambrisentan, macitentan, iloprost, treprostinil, sildenafil, and riociguat may be considered under pharmacy benefits, as determined by each individual Plan. Benefit or contract language describing the “least costly alternative” may apply to the choice of therapy among epoprostenol, bosentan, ambrisentan, macitentan, iloprost, or treprostinil. A generic formulation of epoprostenol is available.

Patients treated with infusion pumps may require a backup pump. However, the cost of a backup pump may be included in the home infusion therapy charges or in the HCPCS code (see Codes section).

Sildenafil citrate is available as Revatio and Viagra. Benefit or contract language describing the “least costly alternative” may apply to this choice. Pricing differences may exist between alternatives. Revatio is available as a 10- and 20-mg tablet. Viagra is available in 25-, 50-, and 100-mg tablets. Generic sildenafil is available.

Tadalafil is available as Cialis and Adcirca. Benefit or contract language describing the "least costly alternative" may apply to this choice. Pricing differences may exist between alternatives. Cialis is available as 2.5-, 5-, 10-, 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).

**BACKGROUND**

**PHARMACOLOGIC THERAPIES FOR PULMONARY HYPERTENSION**

This evidence review addresses advanced pharmacologic therapies for pulmonary hypertension (PH). Advanced pharmacologic therapies are newer specialty pharmacy drugs specifically intended to impact the natural history of PH, rather than supportive medications that treat disease manifestations. These newer specialty pharmacy drugs have been approved by the U.S. Food and Drug Administration (FDA) only for a subset of classes of PH (World Health Organization [WHO] groups 1 and 4, discussed below); as a result, BCBSA only addresses classes of PH for which advanced pharmacologic therapies are approved.

**Pulmonary Hypertension**

**Classification**

The 2013 WHO classification of PH, which is based on the consensus of an international group of experts at the Fifth World Symposium on Pulmonary Hypertension, is the most widely used system used in clinical care and research.¹ There are 5 WHO categories of PH:

- Group 1: Pulmonary arterial hypertension (PAH)
- Group 2: PH due to left heart disease
- Group 3: PH due to chronic lung disease and/or hypoxemia

• Group 4: PH due to chronic thromboembolic disease (chronic thromboembolic pulmonary hypertension [CTEPH])
• Group 5: PH due to mixed or uncertain causes.

For each category, there are numerous subcategories indicating more specific disease etiologies. For example, in WHO group 1, the most common subcategory is idiopathic PAH, which is a disorder of unknown etiology categorized by abnormal proliferation of blood vessels in the pulmonary arterial system. Other classification systems, such as those developed by the American College of Cardiology Foundation and American Heart Association, are very similar but have differences in the subcategories of group 1.

**Disease Description**
PH is defined as increased arterial pressure in the lung vasculature. Increased pulmonary pressure can be caused by primary abnormalities in the pulmonary vascular system; it can also be caused by other abnormalities in the cardiac or pulmonary organs, which may lead to secondary elevations in pulmonary arterial pressure. A definitive diagnosis of PH is usually made following measurement of pulmonary arterial pressure by right heart catheterization. A pulmonary arterial pressure of at least 25 mm Hg confirms the diagnosis.

Clinical symptoms of PH are related to right-sided heart failure and impaired oxygen delivery by the lungs. Warning signs are nonspecific but often present as a constellation of symptoms including dyspnea on exertion, fatigue, weakness, and syncope. High pulmonary pressures lead to increased work of the right ventricle. This chronic hemodynamic overload leads to low cardiac output and progressive right ventricular dilatation. In advanced disease, signs of right-sided heart failure occur (eg, abdominal distension, hepatic congestion, pedal edema). Without treatment, the disease is progressive and eventually fatal; however, the natural history and rapidity of progression is variable. Premature death most commonly results from complications of right heart failure.

There are also differences in the pathophysiology, clinical manifestations, and natural history of each PH category. Only categories relevant to this evidence review (WHO groups 1 and 4) are discussed herein.

**WHO Group 1 (PAH)**
PAH is characterized pathophysiologically by abnormal proliferation of pulmonary artery smooth muscle cells in the arteries. This causes a decrease in the size of the pulmonary artery lumen, decreased reactivity of the vascular bed, increased pulmonary vascular resistance, and elevated pressure in the pulmonary circulation. Idiopathic PAH is the most common type of PAH and is more prevalent in women than in men. It often affects women in the third or fourth decade, resulting in a very high burden of illness for young, otherwise healthy patients. Median 1-year survival has been estimated to be 85%, and median 5-year survival has been estimated to be 57%.

**WHO Group 4 (CTEPH)**
CTEPH primarily occurs after acute or chronic pulmonary embolism. Progressive pulmonary vascular remodeling (thrombi organization, fibrous stenosis, microvascular changes) obstructs pulmonary arteries, leading to PH and right heart failure. Estimated CTEPH incidence among patients who survive an acute pulmonary embolism ranges from 0.6% to 3.8%. However, many patients have no clinical history of pulmonary embolism, and CTEPH is likely underdiagnosed. The severity and prognosis are variable, depending on the extent of lung damage caused by prior thromboembolism, and the degree to which future episodes can be prevented.
**Treatment**
Conventional therapies considered in all patients with PH regardless of etiology include medications to treat heart failure (diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, digoxin), oxygen therapy, and exercise. Lung transplantation and combined heart-lung transplantation have been performed in patients refractory to medical management. There are also specific therapies for each WHO group. For example, anticoagulation is a treatment option in WHO groups 1 and 4, and both anticoagulation and surgical thrombectomy are treatment options for appropriate patients in group 4.

**Advanced Pharmacologic Therapies**
Advanced pharmacologic therapies for PH are defined as newer specialty pharmacy drugs specifically intended to impact the natural history of PH, rather than treat disease manifestations (see Table 1 for specific agents). These specialty drugs can be administered as single agents or in various combinations. Advanced pharmacologic therapies are FDA-approved for treatment of PH groups 1 and 4; therefore, these classes are discussed further.

**WHO Group 1 (PAH)**
Table 1 lists the classes of medications with FDA approvals for treatment of PAH.

**Table 1. Approved Medication Classes for Treating Pulmonary Arterial Hypertension**

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin analogues</td>
<td>Prostacyclin is an endogenously produced vasodilator. Analogues of prostacyclin mimic the vasodilatory action of endogenous prostacyclin.</td>
</tr>
<tr>
<td>Prostacyclin receptor agonists</td>
<td>The approved drug in this class, selexipag, and its active metabolite are selective for the IP receptor and thus differ from other prostanoid receptors</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>Endothelin 1 is a potent vasoconstrictor and is found in increased concentrations in the lungs of patients with familial hypercholesterolemia. Endothelin receptor antagonists block the action of endothelin, thus resulting in vasoconstriction.</td>
</tr>
<tr>
<td>PDE inhibitors</td>
<td>PDE inhibitors are cyclic guanosine monophosphate inhibitors. Cyclic guanosine monophosphate inhibition results in reduced breakdown and longer duration of nitric oxide, which is a potent vasodilator.</td>
</tr>
<tr>
<td>Soluble guanylate cyclase</td>
<td>Riociguat is a first-in-class oral soluble guanylate cyclase stimulator</td>
</tr>
<tr>
<td>stimulator</td>
<td>IP: prostacyclin receptor, also known as the prostaglandin I2 receptor or IP; PDE: phosphodiesterase.</td>
</tr>
</tbody>
</table>

**WHO Group 4 (CTEPH)**
The single medication currently FDA-approved for treatment of CTEPH is riociguat. Riociguat stimulates soluble guanylate cyclase, both directly and indirectly, by increasing sensitivity of the enzyme to nitric oxide. Thus, riociguat may be effective for conditions in which endogenous nitric oxide (a vasodilator) is depleted.

**REGULATORY STATUS**
Table 2 summarizes advanced therapies for treatment of PAH (WHO group 1) and CTEPH (WHO group 4) and their current regulatory status (see Appendix Tables 1 and 2 for functional classes).
### Table 2. Regulatory Status of Advanced Treatments of PAH and CTEPH

<table>
<thead>
<tr>
<th>Drug (Brand) Name</th>
<th>Manufacturer</th>
<th>FDA Approval Date</th>
<th>Routes of Administration</th>
<th>Dose Range</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostacyclin analogue (ie, prostanoids)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epoprostenol sodium (Flolan®)</td>
<td>GlaxoSmithKline</td>
<td>FDA approved 1995</td>
<td>➢ Continuous IV infusion via central venous catheter using an ambulatory infusion pump</td>
<td>➢ 1-20 ng/kg/min</td>
<td>➢ Treatment of PAH (WHO group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly (97%) patients with NYHA class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with CTD (51%). ➢</td>
</tr>
<tr>
<td>Treprostinil sodium (Remodulin®)</td>
<td>United Therapeutics</td>
<td>FDA approved 2002</td>
<td>➢ Continuous SC infusion ➢ IV infusion (if SC infusion not tolerated) ➢ 0.625-1.25 ng/kg/min</td>
<td></td>
<td>➢ Treatment of PAH (WHO group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with CTD (19%) ➢ ➢ Patients who require transition from epoprostenol sodium (Flolan), to reduce rate of clinical deterioration</td>
</tr>
<tr>
<td>Treprostinil (Tyvaso®)</td>
<td>United Therapeutics</td>
<td>FDA approved 2009</td>
<td>➢ Inhalation via nebulizer; specific to 1 pulmonary drug delivery system ➢ 18-54 μg, 4 times daily</td>
<td></td>
<td>➢ Treatment of PAH (WHO group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with CTD (33%)</td>
</tr>
<tr>
<td>Treprostinil (Orenitram®)</td>
<td>United Therapeutics</td>
<td>FDA approved 2013</td>
<td>➢ Oral ➢ Maximum dose as tolerated: 3.4-21 mg twice dailya</td>
<td></td>
<td>➢ Treatment of PAH (WHO group 1) to improve exercise capacity. Study establishing effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with CTD (19%).</td>
</tr>
<tr>
<td>Iloprost (Ventavis®)</td>
<td>Actelion Pharmaceuticals</td>
<td>FDA approved 2004</td>
<td>➢ Inhalation via nebulizer using a specific pulmonary drug delivery system ➢ 2.5-5 μg, 6-9 times daily</td>
<td></td>
<td>➢ Treatment of PAH (WHO group 1) to improve a composite end point consisting of exercise tolerance, symptoms (NYHA class), and lack of deterioration. Studies establishing effectiveness predominately included patients with NYHA class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with CTD (23%).</td>
</tr>
<tr>
<td>Beraprost</td>
<td>NOT APPROVED IN U.S. &amp; E.U. Failed reviews</td>
<td></td>
<td>➢ Oral</td>
<td></td>
<td>➢ No FDA-approved indications</td>
</tr>
</tbody>
</table>
### Drug (Brand) Name

**Prostacyclin receptor agonists**

- **Selexipag (Uptravi®)**  
  - Manufacture: Actelion Pharmaceuticals  
  - FDA Approval Date: FDA approved 2015  
  - Routes of Administration: Oral  
  - Dose Range: Starting dose 200 μg twice daily. Increase by 200 μg twice weekly to maximum tolerated dose up to 1600 μg twice daily.  
  - FDA-Approved Indications: Treatment of PAH (WHO group 1) to 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®)**  
    - Manufacture: Actelion Pharmaceuticals  
    - FDA Approval Date: FDA approved 2001  
    - Routes of Administration: Oral  
    - Dose Range: 62.5-125 mg twice daily  
    - FDA-Approved Indications: Treatment of PAH (WHO group 1) to improve exercise ability and decrease clinical worsening. Studies establishing effectiveness predominantly included patients with NYHA class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with CTD (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).

  - **Ambrisentan (Letairis®)**  
    - Manufacture: Gilead Sciences  
    - FDA Approval Date: FDA approved 2007  
    - Routes of Administration: Oral  
    - Dose Range: 5-10 mg daily  
    - FDA-Approved Indications: Treatment of PAH (WHO group 1) to improve exercise ability and delay clinical worsening and in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness predominantly included patients with NYHA class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with CTD (34%).

  - **Macitentan (Opsumit®)**  
    - Manufacture: Actelion Pharmaceuticals  
    - FDA Approval Date: FDA approved 2013  
    - Routes of Administration: Oral  
    - Dose Range: 10 mg daily  
    - FDA-Approved Indications: Treatment of PAH (WHO group 1) to delay disease progression (defined as death, initiation of IV or SC prostanoids, or clinical worsening of PAH [decreased 6-minute walk distance, worsened PAH symptoms, need for additional PAH treatment]). Macitentan also reduced hospitalization for PAH.

### Phosphodiesterase inhibitors
### Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Drug (Brand) Name</th>
<th>Manufacturer</th>
<th>FDA Approval Date</th>
<th>Routes of Administration</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil citrate (Revatio®)</td>
<td>Pfizer Labs</td>
<td>FDA approved 2005</td>
<td>• Oral</td>
<td>• Treatment of PAH (WHO group 1) in adults to improve exercise ability and delay clinical worsening. Studies establishing effectiveness were short-term (12-16 wk), and included predominately patients with NYHA class II-III symptoms. Etiologies were idiopathic (71%) or associated with CTD (25%). • 2012: FDA recommended Revatio not be prescribed to children (ages 1-17 y) for PAH. (Product not approved for treatment of PAH in children.)</td>
</tr>
<tr>
<td>Tadalafil (Adcirca®)</td>
<td>Eli Lilly</td>
<td>FDA approved 2009</td>
<td>• Oral</td>
<td>• Treatment of PAH (WHO group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA class II-III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with CTD (23%).</td>
</tr>
<tr>
<td>Vardenafil (Levitra®)</td>
<td></td>
<td>FDA approved 2003</td>
<td>• Oral</td>
<td>• No FDA-approved indications for PAH or CTEPH</td>
</tr>
<tr>
<td><strong>Soluble guanylate cyclase stimulator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riociguat (Adempas®)</td>
<td>Bayer HealthCare</td>
<td>FDA approved 2013</td>
<td>• Oral</td>
<td>• Treatment of adults with PAH (WHO group 1) to improve exercise capacity and WHO functional class • Treatment of adults with persistent or recurrent CTEPH (WHO group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class</td>
</tr>
<tr>
<td><strong>Tyrosine kinase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imatinib (Gleevec®)</td>
<td></td>
<td>FDA approved 2001</td>
<td>• Oral</td>
<td>• No FDA-approved indications for PAH or CTEPH</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Simvastatin</td>
<td></td>
<td>FDA approved 1991</td>
<td>• Oral</td>
<td>• No FDA-approved indications for PAH or CTEPH</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td></td>
<td>FDA approved 1999</td>
<td>• Oral</td>
<td>• No FDA-approved indications for PAH or CTEPH</td>
</tr>
</tbody>
</table>


* Mean 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.
RATIONALE

This evidence review was created in January 1998 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through August 23, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

PULMONARY ARTERIAL HYPERTENSION MONOTHERAPY USING TYROSINE KINASE INHIBITORS OR STATINS

Clinical Context and Test Purpose
The purpose of monotherapy using tyrosine kinase inhibitors (TKIs) or statins is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with pulmonary arterial hypertension (PAH).

The question addressed in this evidence review is: Does use of monotherapy with TKIs or statins improve the net health outcome in individuals who have PAH?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with PAH.

Interventions
The therapy being considered is monotherapy using TKIs or statins.

TKIs and statins were not developed as PAH-specific therapy, and are not approved by the U.S. Food and Drug Administration (FDA) for treatment of PAH.

Comparators
The following therapies are currently being used to treat PAH: conventional therapy and different PAH-specific drugs.

Outcomes
The general outcomes of interest are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity.
Timing
Follow-up ranges from months to years to monitor outcomes

Setting
Patients with PAH are actively managed by pulmonologists or cardiologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Tyrosine Kinase Inhibitors
No RCTs were identified that evaluated imatinib as monotherapy for patients with PAH. The safety of imatinib in patients with PAH was assessed by Frost et al (2015) in a long-term extension of an RCT of imatinib as add-on third-line therapy. A total of 144 patients entered the extension study (66 patients had been on imatinib for 24 weeks, 78 patients were switching to imatinib from placebo). One hundred thirty-five (94%) of 144 patients discontinued the extension study, and about one-third of the patients discontinued because of adverse events. When the study was terminated (due to high dropout rate), the mean exposure to imatinib was 931 days in the group who took imatinib in the original RCT, and 590 days in the ex-placebo group. Seventeen (12%) of the 144 patients died during the study or within 30 days of leaving it. Serious adverse events (other than death) occurred in 40 (60.6%) patients in the group originally taking imatinib, and 53 (67.9%) in the ex-placebo group. The trialists concluded that imatinib should not be used off-label for treatment of PAH.

Statins
Anand et al (2016) published a systematic review of placebo-controlled RCTs evaluating statins for treating PAH. Reviewers identified 4 RCTs, of which two evaluated simvastatin, one assessed atorvastatin, and one evaluated rosuvastatin. The total sample size was 387; 1 study had 220 patients, and the others had fewer than 100 patients each. The primary outcomes of the review were mortality and change in 6-minute walk distance (6MWD) from baseline to follow-up. A pooled analysis of data from 3 trials did not find a significant benefit of statins on mortality (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.32 to 1.74; $I^2=0\%$). Similarly, a pooled analysis of 3 trials did not find a significant benefit of statins on the 6MWD (weighted mean difference [WMD], -9.27 meters; 95% CI, -27.7 to 9.2 meters; $I^2=1.7\%$).

The largest trial assessed in the Anand systematic review was published by Zeng et al (2012). This was a 6-month, double-blind, placebo-controlled randomized trial of 220 Chinese patients with PAH (83%) or chronic thromboembolic pulmonary hypertension (CTEPH; 6%) in World Health Organization (WHO) functional class II or III. Patients received atorvastatin 10 mg orally daily or matching placebo in addition to supportive care (diuretics, digoxin, warfarin). After 6 months, the mean difference in 6MWD (atorvastatin – placebo) was 2.5 meters (95% CI, -33 to 38 meters). 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, pulmonary vascular resistance [PVR], or mixed venous oxygen saturation). There were 9 (8%) deaths in the atorvastatin group and 11 (10%) deaths in the placebo group (p=0.31). The trialists concluded: “Atorvastatin 10 mg daily has no beneficial effect on the natural history of PAH or CTEPH over 6 months.”

Section Summary: Pulmonary Arterial Hypertension Monotherapy Using Tyrosine Kinase Inhibitors or Statins

There are no RCTs evaluating the efficacy of TKIs for PAH and 4 RCTs on statins for PAH. A meta-analysis of RCTs evaluating statins for PAH did not report significantly better outcomes (ie, mortality, 6MWD) with the study medication than with placebo. For imatinib, a TKI, there are no placebo-controlled studies evaluating efficacy. However, a 2016 safety study identified a high rate of adverse effects in patients who took imatinib.

PAH THERAPY TREATED WITH ADD-ON COMBINATION THERAPIES

Clinical Context and Test Purpose

The purpose of add-on combination therapy using 2 drug classes FDA-approved for treatment of PAH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with PAH and inadequate response to monotherapy.

The question addressed in this evidence review is: Does add-on combination therapy, using 2 drug classes FDA-approved for treatment of PAH, improve the net health outcome in individuals who have PAH and inadequate response to monotherapy?

The following PICOTS were used to select literature to inform this review.

 Patients
The relevant population of interest is individuals with PAH and inadequate response to monotherapy.

 Interventions
The therapy being considered is add-on combination therapy using 2 drug classes FDA-approved for treatment of PAH.

 Comparators
The following therapies are currently being used to treat PAH: different PAH-specific drugs or drug combinations.

 Outcomes
The general outcomes of interest are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity.

 Timing
Follow-up of months to years is of interest to monitor outcomes.

 Setting
Patients with PAH are actively managed by pulmonologists or cardiologists in an outpatient setting.

 Study Selection Criteria
Methodologically credible studies were selected using the following principles:

 - To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

**Systematic Reviews**

Meta-analyses have 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 add-on treatment for patients with an inadequate response to a single medication. (Several trials in the Lajoie et al [2016] meta-analysis included a combination of patients on baseline therapy and treatment-naive patients.) Key recent meta-analyses are described in Table 3.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Studies</th>
<th>Study Eligibility</th>
<th>No. of Studies</th>
<th>Summary of Results (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lajoie et al (2016)</td>
<td>17</td>
<td>• RCTs of PAH-specific combination therapy vs monotherapy in adults</td>
<td>16</td>
<td>All-cause mortality:&lt;br&gt;• RR=0.88 (0.74 to 1.05)&lt;br&gt;Clinical worsening:&lt;br&gt;• RR=0.65 (0.56 to 0.76)&lt;br&gt;Hospitalization:&lt;br&gt;• RR=0.71 (0.53 to 0.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥12 wk in duration</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>McCrory et al (2013)</td>
<td>5 (AHRQ)</td>
<td>• RCTs of PAH-specific combination therapy vs monotherapy</td>
<td>3</td>
<td>All-cause mortality:&lt;br&gt;• OR=0.37 (0.04 to 3.32)&lt;br&gt;6MWD (m):&lt;br&gt;• MD=23.9 (8.0 to 39.9)&lt;br&gt;Hospitalization:&lt;br&gt;• OR=0.64 (0.31 to 1.36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Fox et al (2011)</td>
<td>6</td>
<td>• RCTs of PAH-specific combination therapy vs monotherapy</td>
<td>4</td>
<td>All-cause mortality:&lt;br&gt;• RR=0.42 (0.08 to 2.26)&lt;br&gt;Clinical worsening:&lt;br&gt;• RR=0.42 (0.17 to 1.04)&lt;br&gt;6MWD (m):&lt;br&gt;• MD=25.2 (13.3 to 38.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥12 wk in duration</td>
<td>4</td>
<td></td>
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</tbody>
</table>

AHRQ: Agency for Healthcare Research and Quality; CI: confidence interval; MD: mean difference; OR: odds ratio; PAH: pulmonary arterial hypertension; RCT: randomized controlled trial; RR: relative risk; 6MWD: 6-minute walk distance.

Clinical worsening: Composite outcome defined differently across studies but generally included death, admission to hospital due to worsening PAH, lung transplantation, symptom progression, and treatment escalation.

These meta-analyses of add-on combination therapy had mixed findings but generally found improvements in some outcomes compared with a single medication. The most recent and comprehensive meta-analysis found significantly lower rates of hospitalizations and less clinical worsening with the addition of a second class of medications compared with a single medication. Several meta-analyses found significantly greater exercise capacity, as measured by 6MWD with add-on combination therapy; however, the additional distance walked may not be clinically significant. The 2013 Agency for...
MP 5.01.509
Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

Healthcare Research and Quality comparative effectiveness review by McCrory et al (2013) indicated that 33 meters is generally considered the minimally important difference in distance walked in 6MWD. None of the meta-analyses found significantly less all-cause mortality with add-on combination therapy.

Randomized Controlled Trials
RCTs have evaluated various medication combinations for treating PAH. These combinations include, but are not limited to prostacyclin analogues and endothelin receptor antagonists, phosphodiesterase (PDE) inhibitors and endothelin receptor antagonists, and prostacyclin analogues and PDE inhibitors. An RCT evaluating riociguat plus sildenafil (PDE type 5 [PDE5] inhibitors) concluded that this combination is contraindicated.

Section Summary: Therapy Using Add-On Combination Therapies
Numerous RCTs of different combinations of medication and meta-analyses of RCTs have been conducted. In all RCTs included in the 2016 meta-analysis, the combination therapy involved drugs from different classes, although the specific combination of riociguat and PDE5 inhibitors is contraindicated. The 2016 meta-analysis is the most recent and comprehensive. It included 17 RCTs of add-on combination therapy vs monotherapy, with at least 12 weeks of follow-up; while mortality rates did not differ significantly between the 2 groups, the meta-analysis reported significantly lower rates of clinical worsening and hospitalizations for the group receiving combination therapy.

PAH THERAPY USING INITIAL COMBINATION THERAPIES

Clinical Context and Test Purpose
The purpose of initial combination therapy using 2 drug classes FDA-approved for treatment of PAH is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with PAH.

The question addressed in this evidence review is: Does initial combination therapy, using 2 drug classes FDA-approved for treatment of PAH, improve the net health outcome in individuals who have PAH?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with PAH.

Interventions
The therapy being considered is initial combination therapy using 2 drug classes FDA-approved for treatment of PAH.

Comparators
The following therapeutic strategy is currently being used to treat PAH: initial monotherapy, followed by combination therapy if monotherapy fails.

Outcomes
The general outcomes of interest are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity.

Timing
Follow-up from months to years is of interest to monitor outcomes.
Setting
Patients with PAH are actively managed by pulmonologists or cardiologists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
Two RCTs specifically evaluating initial combination therapy in patients with PAH were identified.

The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial, reported by Galie et al (2015) randomized patients to initial treatment with ambrisentan (an endothelin receptor antagonist), tadalafil (a PDE inhibitor), or a combination of these 2 medications. A total of 610 adults ages 18 to 75 years with WHO functional class II or III symptoms of WHO group 1 PAH underwent randomization, but the entry criteria changed during the trial. The primary end point was the first event of clinical failure in a time-to-event analysis. Clinical failure was a composite end point including death, hospitalization for worsening PAH, disease progression, and unsatisfactory long-term clinical response. Mean duration of trial participation in the 500 patients included in the primary analysis set was 609 days. In these patients, the primary end point of clinical failure occurred in 46 (18%) of 253 patients in the combination therapy group, in 43 (34%) of 126 in the ambrisentan group, and in 34 (28%) of 121 in the tadalafil group. The clinical failure rate was significantly lower in the combined treatment group than in the ambrisentan group (p<0.001) or the tadalafil group (p=0.005). Serious adverse events among patients in the primary analysis set occurred in 92 (36%) patients in the combined treatment group, 45 (36%) patients in the ambrisentan group, and 50 (41%) patients in the tadalafil group (not significantly different among groups).

The Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH (BREATH-2) trial, reported by Humbert et al (2004) compared epoprostenol alone with the combination of epoprostenol plus bosentan. 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 trial. At 16 weeks, mean change in total pulmonary resistance did not differ significantly between groups (-36.3 dyns⁻¹ cm⁻⁵ ± 4.3% in the combination treatment group vs -22.6 dyns⁻¹ cm⁻⁵ ± 4.3% in the epoprostenol plus placebo group, p=0.08). Secondary outcomes also did not differ significantly between groups. For example, the median 6MWD increased 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).
Section Summary: PAH Therapy Using Initial Combination Therapies
Two RCTs have compared 6 months of initial combination therapy vs monotherapy for PAH. In 1 trial, among patients in the primary analysis set, there was a significantly lower rate of clinical failure at 6 months in the combined therapy group than in the monotherapy groups. Rates of adverse events were similar across groups. Data interpretation of this study is difficult because the trialists changed enrollment criteria during the trial and used a complex composite outcome with multiple components. The other RCT did not find significant differences in outcomes between a group receiving initial combined therapy and a group receiving monotherapy at 16 weeks; this study had a small sample size and might have been underpowered for secondary outcomes. Both trials lacked a clinically relevant comparison between initial combination therapy and initial monotherapy followed by combination therapy for patients with an inadequate response.

INOPERABLE CTEPH MONOTHERAPY

Clinical Context and Test Purpose
The purpose of soluble guanylate cyclase stimulator (eg, riociguat) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with inoperable CTEPH or pulmonary hypertension (PH) after surgery.

The question addressed in this evidence review is: Does use of a soluble guanylate cyclase stimulator improve the net health outcome in individuals with inoperable CTEPH or PH after surgery?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are individuals with inoperable CTEPH or PH after surgery.

Interventions
The therapy being considered is a soluble guanylate cyclase stimulator (eg, riociguat).

Comparators
The following therapy is currently being used to treat inoperable CTEPH or PH after surgery: standard of care.

Outcomes
The general outcomes of interest are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity.

Timing
Follow-up over years is of interest to monitor outcomes.

Setting
Patients with inoperable CTEPH or PH after surgery are actively managed by pulmonologists or cardiologists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
• In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
• To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
• Studies with duplicative or overlapping populations were excluded.

**Riociguat**
The pivotal CHEST-1 trial, published by Ghofrani et al (2013), assessed the efficacy and safety of riociguat to treat CTEPH. CHEST-1 was a double-blind RCT in 261 adults who had inoperable CTEPH (n=188 [72%]) or persistent PH after pulmonary endarterectomy (n=73 [28%]). Patients receiving PAH medications were excluded. Three times daily, patients were randomized to placebo or riociguat titrated to 0.5 to 2.5 mg. Doses were 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.

Two hundred forty-two (93%) patients from both groups completed the trial; 77% of completers in the riociguat group continued the maximum dose to week 16. Mean change in 6MWD, the primary efficacy outcome, 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 meters; p<0.001). Results were consistent across multiple sensitivity analyses and predefined subgroups (eg. baseline WHO functional class). Improvements in N-terminal brain natriuretic peptide and WHO functional class were also 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 (vs placebo) 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%), respectively. 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.

Additional data on secondary outcomes from CHEST-1 were published by Kim et al (2017). 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).

CHEST-2 (2015) was an extension study that included patients in CHEST-1 who did not withdraw due to clinical worsening. All patients in CHEST-2 received open-label riociguat. Results of an interim analysis, in which most patients had received one or more years of treatment, were published by Simonneau et al (2015). A total of 243 patients entered CHEST-2 and, at the data cutoff for the analysis, 179 (76%) had received more than 1 year of treatment. The estimated overall survival rate at 1 year was 97% (95% CI, 93% to 98%). In an analysis assuming that all patients who dropped out of the study had died, the estimated 1-year survival rate was 93% (95% CI, 88% to 96%). The rate of clinical worsening-free survival at 1 year was 88% (95% CI, 83% to 92%). Adverse events occurred in 228 (96%) patients, most commonly nasopharyngitis (23%), dizziness (19%), and peripheral edema (18%). Serious adverse events occurred in 100 (42%) patients. Thirteen patient deaths occurred during CHEST-2, none of which was considered drug-related by the investigators.
Section Summary: Inoperable CTEPH Monotherapy
There is only 1 FDA-approved medication for this indication: riociguat. One RCT and its extension study have been published. The RCT, which was double-blind, found that functional outcomes at 16 weeks improved significantly more in the group receiving riociguat. Both groups had a high proportion of adverse events, and 1 death was attributed to riociguat. In the extension study, the estimated 1-year survival rate was 97%. Thirteen deaths occurred, none of which was attributed to study medication.

PERIOPERATIVE CTEPH THERAPY

Clinical Context and Test Purpose
The purpose of perioperative prostacyclin analogues, endothelin receptor antagonists, and riociguat is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with operable CTEPH.

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%. The question addressed in this evidence review is: Do use of perioperative prostacyclin analogues, endothelin receptor antagonists, or riociguat improve the net health outcome in individuals who have CTEPH?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with operable CTEPH.

Interventions
The therapies being considered are perioperative prostacyclin analogues, endothelin receptor antagonists, and riociguat.

Comparators
The following therapy is currently being used to treat operable CTEPH: pulmonary endarterectomy alone.

Outcomes
The general outcomes of interest are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity.

Timing
Follow-up of weeks to months is of interest to monitor outcomes.

Setting
Patients with operable CTEPH are actively managed by pulmonologists or cardiologists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought. Studies with duplicative or overlapping populations were excluded.

**Prostacyclin Analogues (Prostanoids)**

**Epoprostenol**
One nonrandomized comparative study was identified. Nagaya et al (2003) reported retrospectively on 33 patients with CTEPH who underwent pulmonary endarterectomy. Twelve patients with preoperative PVR greater than 1200 Wood units received preoperative epoprostenol for a mean of 6 weeks. There were statistically significant reductions in PVR before and after surgery in both groups and no statistically significant difference in PVR between groups at 1 month after surgery (mean PVR, ≈300 Wood units in both groups). The only patient who died within 30 days postsurgery was in the epoprostenol group (overall mortality rate, 3.0%; 8.3% in the epoprostenol group vs 0% in the comparator group).

**Iloprost**
Kramm et al (2003) reported on the effect of inhaled iloprost in the perioperative period. Ten patients with mean PVR of 972 Woods units received inhaled iloprost at 3 time points: immediately before surgery, on admission to the intensive care unit after surgery, and at 12 or more hours postsurgery. 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 PH (10% mortality rate).

**Endothelin Receptor Antagonists**

**Bosentan**
Reesink et al (2010) reported on the results from a single-blind RCT of 26 patients with CTEPH who were eligible for pulmonary endarterectomy. 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 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 of surgery were 9% and 30%, respectively.

**Soluble Guanylate Cyclase Stimulators**

**Riociguat**
No trials evaluating riociguat for preoperative therapy were identified.

**Section Summary: Perioperative CTEPH Treatment**
The few studies, with small numbers of patients and limited comparative data, do not provide sufficient evidence to determine whether mortality and PVR are improved with any of these medications. High-quality RCTs are needed to determine whether perioperative treatment with advanced medications improves outcomes for this population.
SUMMARY OF EVIDENCE

Pulmonary Arterial Hypertension
For individuals who have PAH who receive monotherapy using tyrosine kinase inhibitors or statins, the evidence includes no RCTs on tyrosine kinase inhibitors and 4 RCTs and a meta-analysis on statins. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. A meta-analysis of RCTs evaluating statins for PAH did not find significantly better outcomes (ie, mortality, 6-minute walk distance) with study medication than with placebo. For imatinib (a tyrosine kinase inhibitor), there are no placebo-controlled studies evaluating efficacy. However, a 2016 safety study identified a high rate of adverse events in patients who took imatinib. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have PAH and inadequate response to monotherapy who receive add-on combination therapy using 2 drug classes FDA-approved for treatment of PAH, the evidence includes RCTs and meta-analyses. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The most recent and comprehensive meta-analysis of RCTs was published in 2016. It included 17 RCTs comparing add-on combination therapy with monotherapy with at least 12 weeks of follow-up; the meta-analysis found significantly lower rates of clinical worsening and hospitalizations with add-on combination therapy. Mortality rates did not differ significantly between groups. In all RCTs selected for the 2016 meta-analysis, the combination therapy involved different drug combinations from different classes, although the specific combination of riociguat and phosphodiesterase type 5 inhibitors is contraindicated. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have PAH who receive initial combination therapy using 2 drug classes FDA-approved for treatment of PAH, the evidence includes 2 RCTs. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. In 1 study, among patients in the primary analysis set, there was a significantly a lower rate of clinical failure at 6 months in the combination therapy group than in the monotherapy group. Interpreting this study is difficult because the trialists changed enrollment criteria during the trial and used a complex composite outcome with multiple components. The other RCT did not find significant differences in outcomes between a group receiving initial combination therapy and the group receiving monotherapy at 16 weeks; this study had a small sample size and might have been underpowered to assess secondary outcomes. Trials focusing on the clinically relevant comparison between initial combination therapy and initial monotherapy followed by combination therapy for patients with an inadequate response are lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Chronic Thromboembolic Pulmonary Hypertension
For individuals who have inoperable CTEPH or PH after surgery who receive a soluble guanylate cyclase stimulator (eg, riociguat), the evidence includes 1 RCT. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The double-blind RCT found that functional outcomes at 16 weeks improved significantly more in the group receiving riociguat than placebo. Both groups had a high proportion of adverse events, and 1 death was attributed to riociguat. In an extension study, the estimated 1-year survival rate was 97%. Thirteen deaths occurred, none of which was attributed to study medication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have operable CTEPH who receive perioperative prostacyclin analogues, endothelin receptor antagonists, or riociguat, the evidence includes 1 small RCT on bosentan, retrospective
noncomparative studies on epoprostenol and iloprost, and no trials on riociguat. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The few studies, with small numbers of patients and limited comparative data, do not provide sufficient evidence to determine whether mortality and pulmonary vascular resistance are reduced with any of these medications. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT 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.

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

- The use of riociguat and pulmonary arterial hypertension–specific medications to reduce pulmonary vascular resistance preoperatively in patients with chronic thromboembolic pulmonary hypertension who are candidates for pulmonary endarterectomy. There was consensus among reviewers that riociguat is investigational in this setting and that pulmonary arterial hypertension–specific medications are investigational in this setting.
- The use of riociguat in patients with chronic thromboembolic pulmonary hypertension who are candidates for pulmonary endarterectomy but prefer medical treatment. Results were mixed on this question.

2011 Input
In response to requests, input was received from 4 academic medical centers while this policy was under review in 2011. Input focused on combination therapy. Two 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 centers had mixed input; both thought there were situations when combination therapy is medically necessary.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Pulmonary Arterial Hypertension

American College of Cardiology Foundation et al
In 2009, the American College of Cardiology Foundation and American Heart Association released an expert consensus document on pulmonary hypertension (PH) developed with 3 other medical associations. This 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 PDE5 [phosphodiesterase type 5] inhibitors.” The consensus report also cautioned “against widespread treatment of non-PAH PH” until patient benefit has been proven in clinical trials. On the topic of combination therapy, the authors encouraged enrollment into randomized controlled trials evaluating combination therapy.
European Society of Cardiology and European Respiratory Society

In 2015, the European Society of Cardiology and the European Respiratory Society updated their guidelines on the diagnosis and treatment of PH. Regarding treatment of PAH (WHO group 1), the guidelines described 3 steps involved in treating patients:

Step 1: Taking “general measures (physical activity ... psychosocial support...)” followed by (supportive therapy (oral anticoagulants, diuretics...)) and then referring the patient to a specialty center for acute vasoreactivity testing.
Step 2: Engaging in “initial therapy with high-dose CCD [calcium channel blockers] in vasoreactive patients or drugs approved for PAH in non-vasoreactive patients....”
Step 3: Offering “combinations of approved drugs and lung transplant” as an option for patients who fail to respond to steps 1 and 2.

American College of Chest Physicians

In 2014, the American College of Chest Physicians published guidelines on pharmacologic therapy for PAH in adults. Relevant recommendations include:

- For patients with PAH who are treatment-naive, have WHO functional class II or class III symptoms, and “who are not candidates for CCB therapy or who have failed CCD therapy,” monotherapy with an “approved endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE-5) inhibitor, or ... riociguat.
- For patients with PAH in WHO functional class III “who have evidence of rapid progression of their disease, or ... poor clinical prognosis despite treatment with one or two classes of oral agents,” consideration of the “addition of a parenteral or inhaled prostanoid” is recommended.
- For patients with PAH who are treatment-naive and have WHO functional class IV symptoms, initial “monotherapy with a parenteral prostanoid agent” is recommended. If patients “are unable or do not desire to manage parenteral prostanoid therapy,” combination treatment with “an inhaled prostanoid” and “an ETRA” is recommended.

Chronic Thromboembolic Pulmonary Hypertension

American College of Cardiology Foundation et al

The 2009 American College of Cardiology Foundation expert consensus document on PH, developed with other medical societies, recommended pulmonary endarterectomy for eligible patients with chronic thromboembolic pulmonary hypertension (CTEPH).

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 PH 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.”

European Society of Cardiology and European Respiratory Society

The 2015 guidelines from the European Society of Cardiology and the European Respiratory Society recommended pulmonary endarterectomy for technically operable patients with CTEPH. For symptomatic patients with inoperable CTEPH or who have persistent or recurrent CTEPH after surgery,
riociguat was recommended. The guidelines also stated that off-label use of drugs approved for PAH but not CTEPH “may be considered” for inoperable CTEPH patients.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**

Not applicable.

**MEDICARE NATIONAL COVERAGE**

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

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**

Some currently unpublished trials that might influence this review are listed in Table 4.

**Table 4. Summary of Key Trials**

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<td>NCT01908699</td>
<td>A Multicenter, Double-blind, Randomized, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of Oral BPS-314d-MR added-on to Treprostinil, Inhaled (Tyvaso®) in Subjects With Pulmonary Arterial Hypertension</td>
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<td>NCT02634203</td>
<td>Riociguat Versus Balloon Pulmonary Angioplasty in Non-operative Chronic thromboEmbolic Pulmonary Hypertension (RACE)</td>
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<td>NCT03273257</td>
<td>A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Multicentre, Prospective Study to Assess Efficacy of Riociguat in Patients With Operable CTEPH Prior to Pulmonary Endarterectomy With High Preoperative Pulmonary Vascular Resistance</td>
<td>80</td>
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<td><strong>Chronic thromboembolic pulmonary hypertension</strong></td>
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<td>NCT01416636</td>
<td>A Double Blind Controlled Clinical Study to Investigate the Efficacy and Tolerability of Subcutaneous Treprostinil Sodium in Patients With Severe Non-operative Chronic Thromboembolic Pulmonary Hypertension (CTEPH)</td>
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<tr>
<td><strong>Pulmonary arterial hypertension</strong></td>
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NCT: national clinical trial.

\(^{a}\) Denotes industry-sponsored or cosponsored trial.

**REFERENCES**


**CODES**

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<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>93503</td>
<td>Insertion and placement of flow-directed catheter (eg, Swan-Ganz) for monitoring purposes (ie, as part of dose-ranging study)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J1325</td>
<td>Injection, epoprostenol, 0.5 mg</td>
</tr>
<tr>
<td></td>
<td>J3285</td>
<td>Injection, treprostinil, 1 mg</td>
</tr>
<tr>
<td></td>
<td>K0455</td>
<td>Infusion pump used for uninterrupted parenteral administration of medication (eg, epoprostenol or treprostinil)</td>
</tr>
<tr>
<td></td>
<td>K0730</td>
<td>Controlled dose inhalation drug delivery system</td>
</tr>
<tr>
<td></td>
<td>Q4074</td>
<td>Iloprost, inhalation solution, FDA-approved final product,</td>
</tr>
</tbody>
</table>

---

**Original Policy Date:** January 1998
noncompounded, administered through DME, up to 20 mcg

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S0088</td>
<td>Imatinib, 100 mg</td>
</tr>
<tr>
<td>S0090</td>
<td>Sildenafil citrate, 25 mg</td>
</tr>
<tr>
<td>S0155</td>
<td>Sterile diluant for epoprostenol, 50 ml</td>
</tr>
<tr>
<td>S9347</td>
<td>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</td>
</tr>
</tbody>
</table>

**ICD-10-CM**
- I27.0: Primary pulmonary hypertension
- I27.2-I27.29: Other secondary pulmonary hypertension code range
- I27.89: Other specified pulmonary heart diseases

**ICD-10-PCS**
ICD-10-PCS codes are only used for inpatient services. There is no specific ICD-10-PCS code for the initiation of this therapy.

**Type of service**
- Drug therapy

**Place of service**
- Inpatient, home

**POLICY HISTORY**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/13/14</td>
<td>Replace policy</td>
<td>Policy updated with input from clinical reviewers. The investigational policy statement on preoperative reduction of pulmonary vascular resistance in patients with CTEPH who are candidates for pulmonary endarterectomy modified to include riociguat. PAH classification and references 2, 14, and 42 updated.</td>
</tr>
<tr>
<td>03/12/15</td>
<td>Replace policy</td>
<td>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.</td>
</tr>
<tr>
<td>10/28/15</td>
<td>Replace policy</td>
<td>Added policy statement &quot;Combination therapy with Letairis (ambrisentan) and Adcirca (Tadalafil) for the treatment of pulmonary arterial hypertension (PAH/WHO Group 1) may be considered medically necessary&quot;</td>
</tr>
<tr>
<td>05/19/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 22, 2016; references 7, 15, 27-28, 30, 36, 38-39, 41, 43, and 49 added. Oral selexipag (e.g., Uptravi®) added to medically necessary policy statement.</td>
</tr>
<tr>
<td>06/16/16</td>
<td>Replace policy</td>
<td>Policy statement on single agents approved by FDA for treatment of PAH/WHO group 1 and related material in other sections of the policy removed. The policy no longer addresses single agents approved by FDA for treatment of PAH/WHO group 1.</td>
</tr>
</tbody>
</table>
MP 5.01.509
Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/22/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho policy annual review; no change to policy statement.</td>
</tr>
<tr>
<td>12/27/17</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, policy statement remains unchanged. Policy updated with literature review through August 24, 2017; references 10, 22, and 24 added.</td>
</tr>
<tr>
<td>04/30/18</td>
<td>Update only</td>
<td>Medical policy renumbered from 5.01.09 to 5.01.509.</td>
</tr>
<tr>
<td>10/18/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 10/18/2018. Policy updated with literature review through August 23, 2018; reference 15 added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

**APPENDIX**

**Appendix Table 1. New York Heart Association Functional Classification**

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with no limitation of activities; they suffer no symptoms from ordinary activities</td>
</tr>
<tr>
<td>II</td>
<td>Patients with slight, mild limitation of activity; they are comfortable with rest or mild exertion</td>
</tr>
<tr>
<td>III</td>
<td>Patients with marked limitation of activity; they are comfortable only at rest</td>
</tr>
<tr>
<td>IV</td>
<td>Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest</td>
</tr>
</tbody>
</table>

**Appendix Table 2. WHO Functional Classification for Pulmonary Arterial Hypertension**

<table>
<thead>
<tr>
<th>Class</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>No limitation of clinical activity; ordinary physical activity does not cause dyspnea or fatigue</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation in physical activity; ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity; less than ordinary physical activity produces dyspnea, fatigue, chest pain, or near-syncope; no symptoms at rest</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to perform any physical activity without symptoms; dyspnea and/or fatigue present at rest; discomfort increased by any physical activity</td>
</tr>
</tbody>
</table>

WHO: World Health Organization.