Advanced Therapies for Pharmacological Treatment of Pulmonary Arterial Hypertension

Policy Number: 5.01.09  Last Review: 01/2018
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Policy
Blue Cross and Blue Shield of Kansas City will provide coverage for the pharmacologic treatment of pulmonary arterial hypertension (PAH) with prostacyclin analogues, endothelin receptor antagonists, or phosphodiesterase type 5 (PDE5) inhibitors when it is determined to be medically necessary because the following criteria are met. Conventional pharmacologic therapies are considered in all patients with PAH regardless of the etiology.

When Policy Topic is covered
The following therapies may be considered medically necessary for the treatment of pulmonary arterial hypertension (PAH/ WHO Group 1):

- epoprostenol sodium (FLOLAN®, VELETRI) continuous IV infusion;
- treprostinil sodium (REMODULIN®) Continuous SC infusion, IV infusion or (TYVASO®) inhalation via nebulizer; Oral treprostinil (ORENITRAM) should only be prescribed by a physician with expertise in treating pulmonary arterial hypertension, including administration of infused prostanoids.
- iloprost (VENTAVIS®) Inhalation via nebulizer; Treatment with iloprost requires the use of a specialized dispensing device.
- bosentan (TRACLEER®) oral;
- ambrisentan (LETAIRIS®) oral;
- sildenafil citrate (REVATIO®) oral
- tadalafil (ADCIRCA®) oral
- vardenafil (LEVITRA®) oral
- riociguat (ADEMPAS®) oral; For combination treatment, riociguat should not be combined with a phosphodiesterase type 5 inhibitor (sildenafil, tadalafil, vardenafil).
- macitentan (OPSUMIT®) oral
- selexipag (UPTRAVI) oral

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

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

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

- 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.

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

When Policy Topic is not covered

Combination therapy as first-line treatment is considered investigational.

Use of other advanced therapies for the pharmacologic treatment of 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.

The use of epoprostenol, treprostinil, iloprost, bosentan, ambrisentan, macitentan, sildenafil, tadalafil and vardenafil is considered investigational for the treatment of pulmonary hypertension (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)

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 pulmonary hypertension (WHO groups 2, 3, and 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);
- Miscellaneous group (i.e, sarcoidosis, histiocytosis X, lymphangiomatosis).

Considerations

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

Description of Procedure or Service

Pulmonary hypertension (PH) is a chronic, progressive condition characterized by abnormally high pulmonary vascular pressure. Advanced therapies for PH are specialty medications intended to alter the natural history of the disease. These drugs have been approved by the U.S. Food and Drug Administration (FDA) for 2 classes of PH: pulmonary arterial hypertension (PAH; World Health Organization [WHO] group 1), and chronic thromboembolic pulmonary hypertension (CTEPH; WHO...
group 4). PAH is a rare and debilitating disease associated with abnormal proliferation of smooth muscle cells in the pulmonary arterial system, causing progressive right ventricular dilation and low cardiac output. Several advanced therapy medications are approved for PAH and they can be used as single agents or in combination. CTEPH is characterized by residual organized thrombi obstructing the pulmonary vasculature following acute or chronic pulmonary embolism. Currently, the soluble guanylate cyclase stimulator, riociguat is the only medication that has FDA-approval for treatment of CTEPH.

For individuals who have PAH who receive monotherapy using tyrosine kinase inhibitors (TKIs) or statins, the evidence includes a randomized controlled trial (RCT) on each of 2 statins. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The RCTs did not report significantly better outcomes for the statin groups than for the control groups. For imatinib, a TKI, there are no RCTs evaluating efficacy. A 2016 safety study identified a high rate of adverse effects in patients who took imatinib. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have PAH who receive add-on combined therapy using 2 drug classes FDA-approved for treatment of pulmonary arterial hypertension, 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 of add-on combination therapy versus monotherapy with at least 12 weeks of follow-up; the meta-analysis found significantly lower rates of clinical worsening and hospitalization 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have PAH who receive initial combined therapy using 2 drug classes FDA-approved for treatment of pulmonary arterial hypertension, the evidence includes 1 RCT. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The RCT compared initial monotherapy and initial combination therapy. RCTs are lacking on the more clinically relevant comparison (ie, initial combination therapy vs combination therapy) only for those with an inadequate response to initial combination therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have 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 qualitatively 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.
Background

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 drugs are currently approved by the U.S. Food and Drug Administration (FDA) only for a subset of classes of PH (groups 1 and 4); as a result, we will only address classes of PH for which advanced pharmacologic therapies are approved.

PULMONARY HYPERTENSION

Classification

The 2013 World Health Organization (WHO) classification of PH, which is based on the consensus of an international group of experts at the 5th 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: Pulmonary hypertension due to left heart disease
- Group 3: Pulmonary hypertension due to chronic lung disease and/or hypoxemia
- Group 4: Pulmonary hypertension due to chronic thromboembolic disease (chronic thromboembolic pulmonary hypertension [CTEPH])
- Group 5: Pulmonary hypertension due to mixed or uncertain causes.

For each of these categories, there are numerous subcategories indicating more specific disease etiologies. For example, in WHO group 1, the most common subcategory is idiopathic pulmonary arterial hypertension (IPAH), 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.² Increased pulmonary pressure can be caused by primary abnormalities in the pulmonary vascular system, or can be caused by other abnormalities in the cardiac or pulmonary organs that 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.³

Clinical symptoms of PH are related to right-sided heart failure and impaired oxygen delivery by the lungs. They are nonspecific, but often present as a constellation of symptoms including dyspnea on exertion, fatigue, weakness, and syncope.⁵ High pulmonary pressures lead to increased work of the right ventricle. This chronic hemodynamic overload leads in turn to low cardiac output and progressive right ventricular dilatation. In advanced disease, signs of right-sided heart failure occur, such as abdominal distension, hepatic congestion, and pedal edema. Without treatment, the disease is progressive and eventually fatal, although 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 of the different PH categories. We discuss them for the categories included in this evidence review (WHO groups 1 and 4).
**WHO Group 1 (Pulmonary Arterial Hypertension)**

Pulmonary arterial hypertension is characterized pathophysiologically by abnormal proliferation of pulmonary artery smooth muscle cells in the arteries.\(^2\) This 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. IPAH 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%.\(^4\)

**WHO Group 4 (Chronic Thromboembolic Pulmonary Hypertension)**

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.\(^2,5\) Estimated CTEPH incidence among patients who survive an acute pulmonary embolism ranges from 0.6% to 3.8%.\(^2,6\) 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.\(^7\)

**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 medications 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 are the classes that will be discussed further.

**WHO Group 1 (Pulmonary Arterial Hypertension)**

The following classes of medications have FDA-approval for treatment of PAH:

- **Prostacyclin analogues.** Prostacyclin is an endogenously produced vasodilator. Analogues of prostacyclin mimic the vasodilatory action of endogenous prostacyclin.

- **Prostacyclin receptor agonists:** The approved drug in this class, selexipag, and its active metabolite are selective for the IP receptor and thus differ from other prostanoid receptors.

- **Endothelin receptor antagonists.** 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.

- **Phosphodiesterase (PDE) inhibitors.** PDE inhibitors are cyclic guanosine monophosphate (GMP) inhibitors. Cyclic GMP inhibition results in reduced breakdown and longer duration of nitric oxide, which is a potent vasodilator.

- **Soluble guanylate cyclase stimulator:** Riociguat is a first-in-class oral soluble guanylate cyclase stimulator.
**WHO Group 4 (Chronic Thromboembolic Pulmonary Hypertension)**

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.\(^8\)

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

<table>
<thead>
<tr>
<th>Advanced Therapy</th>
<th>Drug</th>
<th>Brand Name</th>
<th>Manufacturer</th>
<th>FDA approval date</th>
<th>Route(s) of Administration</th>
<th>Dose range</th>
<th>FDA Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin Analogues (ie, prostanoids)</td>
<td>epoprostenol sodium (FLOLAN(^\text{®}))</td>
<td>GlaxoSmithKline FDA approved 1995</td>
<td>Continuous intravenous (IV ) infusion via central venous catheter using an ambulatory infusion pump</td>
<td>1 to 20 ng/kg/min</td>
<td>Treatment of PAH (WHO group 1) to improve exercise capacity. Studies establishing effectiveness included predominately (97%) patients with NYHA class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with CTD (51%)</td>
<td></td>
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<tr>
<td></td>
<td>treprostinil sodium (REMODULIN(^\text{®}))</td>
<td>United Therapeutics Corp. FDA approved 2002</td>
<td>Continuous subcutaneous (SC) infusion IV infusion (if SC infusion not tolerated) 0.625 to 1.25 ng/kg/min</td>
<td>Inhalation via nebulizer; specific to one pulmonary drug delivery system 18-54 mcg, 4 times/day</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in patients with NYHA Class II-IV symptoms, to diminish symptoms associated with exercise. Patients who require transition from Flolan, to reduce the rate of clinical deterioration.</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>
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<td></td>
<td>iloprost (VENTAVIS(^\text{®}))</td>
<td>Actelion, Ltd. FDA approved 2004</td>
<td>Inhalation via nebulizer; either of two pulmonary drug delivery devices 2.5 to 5 mcg, 6-9 times/day</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>
<td></td>
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<tr>
<td></td>
<td>Treprostinil (Orenitram)</td>
<td>United Therapeutics FDA Approved 2013</td>
<td>Oral Maximum dose as tolerated; 3.4 – 21mg twice daily</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%)</td>
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</table>
beraprost  
NOT APPROVED IN US & EU  
Failed reviews  
Approved in Japan for treatment of PAH  
oral  
No FDA-approved indications for PAH.

Prostacyclin Receptor Agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Type</th>
<th>Dosage/Details</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selexipag (Uptravi)</td>
<td>Oral Prostacyclin Receptor</td>
<td>Oral</td>
<td>starting dose 200mcg twice daily. Increase by 200mcg twice weekly to maximum tolerated dose up to 1600 mcg twice daily.</td>
<td>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.</td>
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Endothelin Receptor Antagonists

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<tr>
<th>Drug</th>
<th>Class</th>
<th>Type</th>
<th>Dosage/Details</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>bosentan (TRACLEER®)</td>
<td>Oral Endothelin Receptor</td>
<td>Oral</td>
<td>62.5 to 125 mg 2 times/day</td>
<td>Treatment of PAH (WHO group 1) to improve exercise ability and to 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%).</td>
</tr>
<tr>
<td>ambrisentan (LETAIRIS®)</td>
<td>Oral Endothelin Receptor</td>
<td>Oral</td>
<td>5-10 mg/day</td>
<td>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%).</td>
</tr>
<tr>
<td>macitentan (Opsumit)</td>
<td>Oral Endothelin Receptor</td>
<td>Oral</td>
<td>10mg daily</td>
<td>Treatment of PAH (WHO group 1) to delay disease progression (defined as death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH [decreased 6-minute walk distance, worsened PAH symptoms, and need for additional PAH treatment]). Macitentan also reduced hospitalization for PAH.</td>
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Phosphodiesterase (PDE5) Inhibitors

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<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Type</th>
<th>Dosage/Details</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil citrate (REVATIO®)</td>
<td>Phosphodiesterase (PDE5) Inhibitors</td>
<td>Oral</td>
<td>20 mg 3 times/day</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%). August 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>Phosphodiesterase (PDE5) Inhibitors</td>
<td>Oral</td>
<td>40 mg once/day</td>
<td>Treatment of PAH (WHO group 1) to improve exercise ability. Studies establishing effectiveness predominantly 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</td>
<td>Phosphodiesterase (PDE5) Inhibitors</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH. One randomized trial outside of U.S.</td>
<td>No FDA-approved indications for PAH. One randomized trial outside of U.S.</td>
</tr>
</tbody>
</table>

Etiologies:  
- idiopathic or heritable PAH  
- PAH associated with CTD (19%)  
- PAH associated with congenital heart disease with left-to-right shunts (18%)
Soluble Guanylate Cyclase Stimulator

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riociguat (Adempas)</td>
<td>Oral 0.5-2.5mg 3 times daily</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>
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Tyrosine Kinase Inhibitors

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<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (Gleevec)</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH or CTEPH</td>
</tr>
</tbody>
</table>

Statins

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<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Indications</th>
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<tbody>
<tr>
<td>Simvastatin</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH or CTEPH</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH or CTEPH</td>
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It is important to emphasize that the approved treatments for pulmonary arterial disease (PAH; WHO Group 1) have serious side effects and have not shown to be effective in patients with other forms of pulmonary hypertension.

Rationale

This policy was originally created in 1998 and was updated regularly with searches of the MEDLINE database. The most recent literature search was performed through March 22, 2016. Following is a summary of the key literature to date.

Pulmonary Arterial Hypertension Monotherapy Using Tyrosine Kinase Inhibitors or Statins

These agents were not developed as pulmonary arterial hypertension (PAH) specific therapy, and are not -approved by the U.S. Food and Drug Administration (FDA) for treatment of PAH.

Tyrosine Kinase Inhibitors

**Imatinib**

No randomized controlled trials (RCTs) were identified that evaluated imatinib as monotherapy for patients with PAH. 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 who had been on imatinib for 24 weeks, 78 who were switching to imatinib from placebo). One hundred thirty-five (94%) of 144 patients discontinued the extension study and about one-third of them discontinued due to adverse events. When the study was terminated (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

**Simvastatin**

In 2011, Kawut et al evaluated simvastatin and aspirin, alone and together, for treating PAH. This RCT 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 improve the primary outcome (change in the 6-minute walk distance [6MW] at 6 months) compared with aspirin or placebo, and the study was terminated. This study represents insufficient evidence that simvastatin is an effective treatment for PAH.
Atorvastatin

In 2012, Zeng et al published 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.11 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% confidence interval [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 authors 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 tyrosine kinase inhibitors for PAH and 1 RCT on each of 2 statins (simvastatin, atorvastatin). The RCTs did not report significantly better outcomes with study medication than with the control group for either statin. 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 effects in patients who took imatinib.

PAH Therapy Using Add-On Combination Therapies

RCTs have evaluated various medication combinations for treating PAH. These combinations include, but are not limited to prostacyclin analogues and endothelin receptor antagonists,12-14 phosphodiesterase (PDE) inhibitors and endothelin receptor antagonists,15 and prostacyclin analogues and PDE inhibitors.12,16 An RCT evaluating riociguat plus sildenafil (PDE5 inhibitors) concluded that this combination is contraindicated.17

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 meta-analysis18 included a combination of patients on baseline therapy and treatment-naive patients.)

These meta-analyses of add-on combination therapy had mixed findings but generally found improvement in some outcomes compared to a single medication. The most recent and comprehensive meta-analysis found significantly favor 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. However, the additional distance walked may not be clinically significant. The AHRQ comparative effectiveness review (McCrory et al) states that 33 meters is generally considered the minimally important difference (MID) in distance walked in 6MWD.19 None of the meta-analyses found significantly less all-cause mortality with add-on combination therapy.

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. This meta-analysis is the most recent and comprehensive. It included 17 RCTs of add-on combination therapy versus monotherapy with at least 12 weeks of follow-up, and reported significantly lower rates of clinical worsening and hospitalizations for the group receiving combination therapy. Mortality rates did not differ significantly between the 2 groups.
PAH Therapy Using Initial Combination Therapies

One RCT specifically evaluating initial combination therapy in patients with PAH was identified. This 2015 study, the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial, 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 researchers (Galie et al) changed the study entry criteria during the study. 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 study 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, 43 (34%) of 126 in the ambrisentan group, and 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).

Section Summary: PAH Therapy Using Initial Combination Therapies

One RCT has compared 6 months of initial combination therapy versus monotherapy for PAH. Among patients in the primary analysis set, there was a significantly lower rate of clinical failure in the combined therapy group than in the monotherapy groups. Rates of adverse events were similar across groups. Interpreting this study is difficult because the trialists changed entry criteria during the trial and used a complex composite outcome with multiple components. Moreover, trials are lacking on the more clinically relevant comparison of initial combination therapy versus initial monotherapy followed by combination therapy for patients with an inadequate response.

CTEPH Monotherapy

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. Patients were randomized to placebo or riociguat titrated to 0.5 to 2.5 mg 3 times daily. 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%) of 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 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 PVR, 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.

CHEST-2, published in 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 1 or more years of treatment, were published by Simmoneau et al.\textsuperscript{23} 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 patients died during CHEST-2, none of which was considered drug-related by the investigators.

Section Summary: 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. There was a high proportion of adverse events in both groups, and 1 death 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.

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\%.\textsuperscript{24}

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.\textsuperscript{24} Twelve patients with preoperative PVR greater than 1200 Wood units received preoperative epoprostenol for a mean of 6±2 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

In 2003, Kramm et al reported on the effect of inhaled iloprost in the perioperative period.\textsuperscript{25} 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

In 2010, Reesink et al reported results of a single-blind RCT of 26 patients with CTEPH who were eligible for pulmonary endarterectomy.\textsuperscript{26} 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.
Soluble Guanylate Cyclase Stimulators

**Riociguat**

There are no trials evaluating riociguat for preoperative therapy.

**Section Summary: CTEPH Perioperative 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**

For individuals who have pulmonary arterial hypertension (PAH) who receive monotherapy using tyrosine kinase inhibitors (TKIs) or statins, the evidence includes a randomized controlled trial (RCT) on each of 2 statins. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The RCTs did not report significantly better outcomes for the statin groups that for the control groups. For imatinib, a TKI, there are no RCTs evaluating efficacy. A 2016 safety study identified a high rate of adverse effects 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 combined therapy using 2 drug classes approved by the U.S. Food and Drug Administration (FDA) for treatment of pulmonary arterial hypertension, 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 of add-on combination therapy versus monotherapy with at least 12 weeks of follow-up; the meta-analysis found significantly lower rates of clinical worsening and hospitalization 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have PAH who receive initial combined therapy using 2 drug classes FDA-approved for treatment of pulmonary arterial hypertension, the evidence includes 1 RCT. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The RCT compared initial monotherapy and initial combination therapy. RCTs are lacking on the more clinically relevant comparison (ie, initial combination therapy vs combination therapy) only for those with an inadequate response to initial combination therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have CTEPH or pulmonary hypertension 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.
For individuals who have operable chronic thromboembolic pulmonary hypertension (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.

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>

WHO Functional Classification for Pulmonary Arterial Hypertension (World Health Organization)

<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>

References:
Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<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 (e.g., Swan-Ganz) for monitoring purposes (i.e., as part of dose-ranging study)</td>
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<tr>
<td>ICD-9 Procedure</td>
<td>416.0</td>
<td>Primary pulmonary hypertension</td>
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<tr>
<td>ICPC-9 Procedure</td>
<td>416.8</td>
<td>Secondary pulmonary hypertension</td>
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<tr>
<td>HCPCS</td>
<td>J1325</td>
<td>Injection, epoprostenol, 0.5 mg</td>
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<tr>
<td></td>
<td>J3285</td>
<td>Injection, treprostinil, 1 mg</td>
</tr>
<tr>
<td></td>
<td>J7686</td>
<td>Treprostinil, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, 1.74 mg</td>
</tr>
<tr>
<td></td>
<td>K0455</td>
<td>Infusion pump used for uninterrupted parenteral administration of medication (e.g., 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, noncompounded, administered through DME, up to 20 mcg</td>
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<tr>
<td></td>
<td>S0088</td>
<td>Imatinib, 100 mg</td>
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<tr>
<td></td>
<td>S0090</td>
<td>Sildenafil citrate, 25 mg</td>
</tr>
<tr>
<td></td>
<td>S0155</td>
<td>Sterile diluant for epoprostenol, 50 ml</td>
</tr>
<tr>
<td>S9347</td>
<td></td>
<td>Home infusion therapy, uninterrupted, long-term, controlled rate intravenous or subcutaneous infusion therapy (e.g., epoprostenol); administrative services, professional pharmacy services, care coordination, all necessary supplies and equipment (drugs and nursing visits coded separately), per diem</td>
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<td>ICD-10-CM (effective 10/1/14)</td>
<td>I27.0</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>I27.2</td>
<td>Other secondary pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td>I27.89</td>
<td>Other specified pulmonary heart diseases</td>
</tr>
<tr>
<td>ICD-10-PCS (effective 10/1/14)</td>
<td>3E013GC, 3E033GC</td>
<td>Administration, physiological systems and anatomical regions, introduction, percutaneous, other therapeutic substance, code by body part (subcutaneous tissue or peripheral vein)</td>
</tr>
</tbody>
</table>

Type of Service: Drug Therapy
Place of Service: Inpatient, Home

Additional Policy Key Words
Policy Number: 5.01.09

Policy Implementation/Update Information

07/2013    New Policy titled Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension
02/2014    Reviewed – no changes made
02/2015    Reviewed – no changes made
02/2016    Reviewed – no changes made
02/2017    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.
01/2018    Reviewed – no changes to policy statement; references updated
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