Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

Policy # 00215
Original Effective Date: 06/17/2009
Current Effective Date: 01/23/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:
- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Pulmonary Arterial Hypertension (WHO Group 1)
Based on review of available data, the Company may consider the following therapies for the treatment of pulmonary arterial hypertension (PAH), World Health Organization (WHO) Group 1, to be eligible for coverage**:

Prostacycline Analogues
- epoprostenol sodium (FLOLAN®‡)
- epoprostenol sodium (VELETRI®‡)
- treprostinil sodium (REMODULIN®‡)
- treprostinil sodium (TYVASO®‡)
- iloprost (VENTAVIS®‡)
- treprostinil sodium (ORENITRAM®‡)

Prostacycline Receptor Agonists
- selexipag (UPTRAVI®)

Endothelin Receptor Antagonists
- bosentan (TRACLEER®)
- ambrisentan (LETAIRIS®)
- macitentan (OPSUMIT®)

Phosphodiesterase Inhibitors
- sildenafil citrate (REVATIO®)
  - Note that a trial and failure (e.g. intolerance or inadequate response) of generic sildenafil tablets for the treatment of PAH will be required prior to the use of brand REVATIO TABLETS unless there is clinical evidence or patient history that suggests the use of generic sildenafil tablets for the treatment of PAH will be ineffective or cause an adverse reaction to the member.
  (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).

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- tadalafil (ADCIRCA®‡)
  - Note that a trial and failure (e.g. intolerance or inadequate response) of generic tadalafil for the treatment of PAH will be required prior to the use of brand ADCIRCA unless there is clinical evidence or patient history that suggests the use of generic tadalafil for the treatment of PAH will be ineffective or cause an adverse reaction to the member. (Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).

Guanylate Cyclase Stimulator
- riociguat (ADEMPAS®‡)

Chronic Thromboembolic Pulmonary Hypertension (WHO Group 4)
Based on review of available data, the Company may consider riociguat (ADEMPAS) for the treatment of persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4) after surgical treatment OR inoperable CTEPH to be eligible for coverage**.

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of brand REVATIO TABLETS when the patient has NOT tried and failed generic sildenafil tablets for the treatment of PAH to be not medically necessary**.

Based on review of available data, the Company considers the use of brand ADCIRCA when the patient has NOT tried and failed generic tadalafil for the treatment of PAH to be not medically necessary**.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of epoprostenol (FLOLAN/VELETRI), treprostinil (REMODULIN/TYVASO/ORENITRAM), iloprost (VENTAVIS), bosentan (TRACLEER), ambrisentan (LETAIRIS), macitentan (OPSUMIT), sildenafil citrate (REVATIO), selexipag (UPTRAVI), or tadalafil (ADCIRCA) for the treatment of non-pulmonary arterial hypertension (non-PAH) pulmonary hypertension (PH) conditions (WHO Groups 2-5) to be investigational*, including but not limited to the following:
- PH associated with left heart diseases; OR
- PH associated with lung diseases and/ or hypoxemia (including chronic obstructive pulmonary disease); OR
- PH due to chronic thrombotic and/or embolic disease; OR
- Miscellaneous group (i.e., sarcoidosis, histiocytosis X and lymphangiomatosis)

*Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.

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Based on review of available data, the Company considers the use of riociguat (ADEMPAS) for any non-U.S. Food and Drug Administration (FDA)-approved indication to be investigational.*

Based on review of available data, the Company considers the use of tadalafil (CIALIS®‡), vardenafil (LEVITRA®‡), and sildenafil (VIAGRA®‡) for the treatment of PAH (WHO Group 1) and non-PAH PH conditions (WHO Groups 2-5) to be investigational.*

**Background/Overview**

**Pulmonary Hypertension Classification**

The 2013 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. There are 5 WHO categories of PH:

- **Group 1**: 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 (CTEPH);
- **Group 5**: PH 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. 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.

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. 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)**

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 (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%.

**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. 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 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.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
Table 1 summarizes advanced therapies for treatment of PAH (WHO group 1) and CTEPH (WHO group 4) and their current regulatory status (see below Table 1 for functional class descriptions).

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Route(s) of Administration</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin analog</td>
<td>Continuous intravenous infusion via central venous catheter using an ambulatory infusion pump</td>
<td>Treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA functional class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with CTD (51%).</td>
</tr>
<tr>
<td>Epoprostenol sodium (Flolan) GlaxoSmitKline FDA approved 1995</td>
<td>1-20 ng/kg/min</td>
<td></td>
</tr>
<tr>
<td>Treprostinil sodium (Remodulin) United Therapeutics FDA approved 2002</td>
<td>Continuous SC infusion Intravenous infusion (if SC infusion not tolerated) 0.625-1.25 ng/kg/min</td>
<td>Treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA functional 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 Flolan, to reduce the rate of clinical deterioration</td>
</tr>
<tr>
<td>Treprostinil (Tyvaso) United Therapeutics</td>
<td>Inhalation via nebulizer;</td>
<td>Treatment of PAH (WHO Group 1) to improve exercise</td>
</tr>
</tbody>
</table>

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### Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

#### Prostacyclin receptor agonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>FDA Approval Year</th>
<th>Route</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
<th>Indications and Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treprostinil (Orenitram)</td>
<td>United Therapeutics</td>
<td>2009</td>
<td>Oral</td>
<td>18-54 μg, 4 times daily</td>
<td>Treatment of PAH (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with CTD (19%).</td>
<td></td>
</tr>
<tr>
<td>Iloprost (Ventavis)</td>
<td>Actelion Pharmaceuticals</td>
<td>2004</td>
<td>Inhalation via nebulizer using a specific pulmonary drug delivery system</td>
<td>2.5-5 μg, 6-9 times daily</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 functional class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with CTD (23%).</td>
<td></td>
</tr>
<tr>
<td>Beraprost</td>
<td>NOT APPROVED IN U.S. &amp; E.U. Failed reviews Approved in Japan for treating PAH</td>
<td></td>
<td>Oral</td>
<td></td>
<td>No FDA-approved indications for PAH</td>
<td></td>
</tr>
<tr>
<td>Selexipag (Uptravi)</td>
<td>Actelion Pharmaceuticals</td>
<td>2015</td>
<td>Oral</td>
<td>Starting dose 200 mcg twice daily. Increase by 200 mcg twice weekly to maximum dose as tolerated up to 1600 mcg twice daily.</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

#### Endothelin receptor antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>FDA Approval Year</th>
<th>Route</th>
<th>Starting Dose</th>
<th>Maximum Dose</th>
<th>Indications and Dosing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan (Tracleer)</td>
<td>Actelion Pharmaceuticals</td>
<td>2001</td>
<td>Oral</td>
<td>62.5-125 mg 2 times daily</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 functional 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>
<td></td>
</tr>
<tr>
<td>Ambrisentan (Letairis)</td>
<td>Gilead Sciences</td>
<td>2007</td>
<td>Oral</td>
<td>5-10 mg daily</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>
<td></td>
</tr>
<tr>
<td>Macitentan (Opsumit)</td>
<td>Actelion Pharmaceuticals</td>
<td>2013</td>
<td>Oral</td>
<td>10 mg 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]).</td>
<td></td>
</tr>
</tbody>
</table>

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Macitentan also reduced hospitalization for PAH.

**Phosphodiesterase inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Approval Year</th>
<th>Dose/Route</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil citrate (Revatio)</td>
<td>Pfizer Labs</td>
<td>2005</td>
<td>Oral 20 mg 3 times daily</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 that Revatio not be prescribed to children (ages 1-17) for PAH. (Product has not been approved for treatment of PAH in children.)</td>
</tr>
<tr>
<td>Tadalafil (Adcirca)</td>
<td>Eli Lilly</td>
<td>2009</td>
<td>Oral 40 mg daily</td>
<td>Treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening. Studies establishing effectiveness predominately included patients with NYHA functional class II-III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with CTD (23%).</td>
</tr>
<tr>
<td>Vardenafil (Levitra)</td>
<td>FDA approved (but not for PAH)</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH. One randomized trial outside of United States</td>
<td></td>
</tr>
</tbody>
</table>

**Soluble guanylate cyclase stimulator**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Manufacturer</th>
<th>Approval Year</th>
<th>Dose/Route</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riociguat (Adempas)</td>
<td>Bayer HealthCare</td>
<td>2013</td>
<td>Oral 0.5-2.5 mg 3 times daily</td>
<td>Treatment of PAH (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening. Treatment of persistent or recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class</td>
</tr>
</tbody>
</table>

**Tyrosine kinase inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval Year</th>
<th>Dose/Route</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (Gleevec&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>FDA approved (but not for PAH)</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH. Two randomized trials as add-on medication.</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>FDA approved (but not for PAH)</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH. One randomized trial with and without aspirin showed no effect on exercise ability.</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>FDA approved (but not for PAH)</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH. One randomized trial showed no clinical benefit compared with placebo.</td>
</tr>
</tbody>
</table>

**Statins**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval Year</th>
<th>Dose/Route</th>
<th>Effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>FDA approved (but not for PAH)</td>
<td>Oral</td>
<td>No FDA-approved indications for PAH. One randomized trial with and without aspirin showed no effect on exercise ability.</td>
</tr>
</tbody>
</table>


<sup>a</sup> 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.

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

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</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>
</tbody>
</table>

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

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

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

Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The most recent literature review for this policy was performed through August 23, 2018. Following is a summary of the key literature to date on agents that are approved by the FDA for treatment of PAH (WHO group 1) and CTEPH (WHO group 4). Some off-label treatments also are discussed for these 2 indications.

Pulmonary Arterial Hypertension Monotherapy With PAH Specific Drugs
Monotherapy for PAH is comprised of a single agent from one of the following classes of advanced therapies: prostacyclin analogs (prostanoids), prostacyclin receptor agonists, endothelin receptor antagonists, phosphodiesterase type 5 (PDE5) inhibitors, or soluble guanylate cyclase inhibitors. Many randomized controlled trials (RCTs) have evaluated the efficacy of monotherapy with advanced medications. Numerous systematic reviews and meta-analyses of these trials have provided the most important evidence on the efficacy of these agents. Three of the most recent and comprehensive of these reviews are discussed below.

Three meta-analyses are summarized in Table 2. These reviews included between 17 and 22 studies of monotherapy with an advanced medication compared to placebo or another PAH-specific medication.

The selection criteria for inclusion and the outcomes reported differed somewhat between each study, but there was a large amount of overlap among those included. The results of combined analysis were consistent in reporting health outcome benefits for all classes of medications reviewed. The improvements reported in the literature included symptoms, exercise tolerance, other health status measures, and
hospitalizations. None of the reviews reported an improvement in mortality associate with use of these drugs.

**Table 2: Key Meta-Analyses of RCTs on PAH Specific Monotherapy**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Eligibility and No. Included Studies</th>
<th>Medication Classes</th>
<th>Summary of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Badiani and Messori (2016)</td>
<td>RCTs of PAH-specific therapy vs placebo or another PAH-specific medication; ≥8 wk in duration • 17 studies</td>
<td>Prostanoids, Prostacyclin receptor agonists, ERA, PDE5, sGCS</td>
<td>Clinical worsening*: Network meta-analysis found each medication class, except prostanoids, was significantly better than placebo. In indirect head-to-head comparisons, there were no statistically significant differences in 1 class vs any other class.</td>
</tr>
<tr>
<td>Zhang et al (2015)</td>
<td>RCTs of oral PAH-specific therapy vs placebo; reported all-cause mortality or clinical worsening • 21 studies</td>
<td>Prostanoids, ERA, PDE5, sGCS</td>
<td>All-cause mortality: • RR=0.82 (95% CI, 0.61 to 1.10) (21 studies) Clinical worsening*: • RR=0.55 (95% CI, 0.47 to 0.64) (21 studies)</td>
</tr>
<tr>
<td>McCrory et al (AHRQ) (2013)</td>
<td>RCTs of PAH-specific therapy vs placebo or standard therapy • 22 studies</td>
<td>Prostanoids, ERA, sGCS</td>
<td>All-cause mortality: • ERA: OR=0.60 (95% CI, 0.23 to 1.59) (6 studies) • PDE5: OR=0.30 (95% CI, 0.08 to 1.11) (4 studies) • Prostanoids: OR=0.52 (95% CI, 0.29 to 0.95) (8 studies) 6MWD (m): • ERA: MD=39.9 (95% CI, 21.4 to 58.4) (6 studies) • PDE5: MD=38.9 (95% CI, 22.0 to 55.9) (4 studies) • Prostanoids: MD=27.9 (95% CI, 10.3 to 45.4) (7 studies) Hospitalization: • ERA: OR=0.34 (95% CI, 0.17 to 0.69) (3 studies) • PDE5: OR=0.48 (95% CI, 0.25 to 0.91) (4 studies) • Prostanoids: OR=0.42 (95% CI, 0.06 to 3.08) (2 studies)</td>
</tr>
</tbody>
</table>

AHRQ: Agency for Healthcare Research and Quality; CI: confidence interval; ERA: endothelin receptor antagonist; MD: mean difference; OR: odds ratio; PAH: pulmonary arterial hypertension; PDE5: phosphodiesterase type 5 inhibitors; RCT: randomized controlled trial; RR: risk ratio; sGCS: soluble guanylate cyclase stimulator; 6MWD: 6-minute walk distance.

*Clinical worsening: Composite outcome defined in Badiani and Messori as 1 of 6 events: death, admission to hospital due to worsening PAH, lung transplantation, worsening World Health Organization functional class, treatment escalation, or interatrial fistulization. The Zhang meta-analysis used the definition of clinical worsening from individual studies so the components varied but generally included items on the above list.

*In the Zhang meta-analysis, outcomes were similar across all trials and in a subanalysis of approved medications and unapproved medications. In this analysis, riociguat, an sGCS, was considered unapproved.

A comprehensive review of the individual RCTs for this question is beyond the scope of this review. Representative RCTs for each of the following medications are cited as follows: prostacyclin analogues (epoprostenol, treprostinil); oral IP prostacyclin receptor agonists (selexipag); endothelin receptor...
antagonists (bosentan, ambrisentan, macitentan); PDE5 inhibitors (sildenafil citrate, tadalafil, vardenafil); and soluble guanylate cyclase stimulators (riociguat).

Section Summary: PAH Monotherapy With PAH-Specific Drugs
Numerous RCTs and meta-analyses of RCTs have been conducted. A 2016 network meta-analysis, including all 5 FDA-approved medication classes, found significantly less clinical worsening with each medication class versus placebo. Another 2016 meta-analysis, which included 4 of the 5 medication classes, found significantly less clinical worsening with study medication (all medications combined) versus placebo and no significant difference between groups in all-cause mortality.

PAH Monotherapy Using Tyrosine Kinase Inhibitors or Statins
These agents were not developed as PAH-specific therapy, and are not FDA-approved for treatment of PAH. However, they have the same intent of other advanced therapy medications, i.e., to alter the natural history of the disease, and therefore they are included in this review.

Tyrosine Kinase Inhibitors

**Imatinib**
No 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 2×2 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 [6MWD] 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 CTEPH (6%) in 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% confidence interval
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[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, 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: PAH 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 Combination Add-On Therapies
RCTs have evaluated various medication combinations for treating PAH. These combinations include, but are not limited to prostacyclin analogues and endothelin receptor antagonists, PDE inhibitors and endothelin receptor antagonists, and prostacyclin analogues and PDE inhibitors. An RCT evaluating riociguat plus sildenafil (PDE5 inhibitors) concluded that this combination is contraindicated.

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-analysis included a combination of patients on baseline therapy and treatment-naive patients.) Key recent meta-analyses are described in Table 3.

Table 3. Key Meta-Analyses of RCTs on Add-On Combination Therapy Versus Monotherapy

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

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Fox et al (2011)  
- RCTs PAH-specific combination therapy vs monotherapy; ≥12 wk in duration  
- 6 studies

All-cause mortality:  
- RR=0.42 (95% CI, 0.08 to 2.26) (4 studies)  
- Clinical worsening*:  
  - RR=0.42 (95% CI, 0.17 to 1.04) (4 studies)  
  - 6MWD (m):  
    - MD=25.2 (95% CI, 13.3. to 38.2) (4 studies)

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: risk ratio; 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 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 Agency for Healthcare Research and Quality (AHRQ) comparative effectiveness review (McCrory et al) states that 33 meters is generally considered the minimally important difference (MID) in distance walked in 6MWD. None of the meta-analyses found significantly less all-cause mortality with add-on combination therapy.

Section Summary: Therapy Using Combination Add-On 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.

Pulmonary Arterial Hypertension Therapy Using Combination Initial 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, (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 Combination Initial 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 a 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.

Chronic Thromboembolic Pulmonary Hypertension Monotherapy

Riociguat
The pivotal CHEST-1 trial (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 (72%) or persistent PH after pulmonary endarterectomy (28%). Patients receiving PAH medications were excluded. Patients were randomized to placebo or riociguat titrated to 0.5 to 2.5 mg three times daily. Dose was optimized during the first 8 weeks, and the optimized dose was continued for 8 additional weeks. The primary efficacy outcome was change in 6MWD at 16 weeks.

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

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. 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.

Chronic Thromboembolic Pulmonary Hypertension 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%.

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±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. 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. 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.

**Clinical Input Received From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**2011 Input**

In response to requests, input was received through 4 academic medical centers while this policy was under review in 2011. The input focused on the issue of combination therapy. Two of the academic medical centers disagreed with the 2010 policy statement that combination therapy is considered investigational (other than when changing from 1 medication to another). The other 2 academic medical centers had mixed input; both thought there were situations in which combination therapy is medically necessary.

**2014 Input**

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

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

**Summary of Evidence**

For individuals who have PAH who receive monotherapy using 1 of 5 classes of drugs FDA-approved for PAH, the evidence includes many RCTs and meta-analyses. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. A 2016 network meta-analysis, including all 5 FDA-approved medication classes, found significantly better outcomes with each medication.
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class than with placebo. Another 2016 meta-analysis, which included 4 of the 5 medication classes, found significantly better outcomes with study medication (all medications combined) than placebo and no significant differences between medication groups in all-cause mortality. 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 monotherapy using TKIs or statins, the evidence includes RCT on each of 2 statins. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The RCTs on statins did not report significantly better outcomes compared to the control group. For imatinib, a tyrosine kinase inhibitor (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 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 of add-on combination therapy versus monotherapy with at least 12 weeks of follow-up; it 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 PDE5 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 PAH, 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 (i.e., 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 (e.g., 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. There was a high proportion of adverse events in both groups and 1 death 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 analogs, 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 morality and PVR improve with any of these medications. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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06/04/2009 Medical Director review
06/17/2009 Medical Policy Committee approval. New Policy.
06/03/2010 Medical Policy Committee review
06/16/2010 Medical Policy Implementation Committee approval. New drug TYVASO added.
06/02/2011 Medical Policy Committee review
06/15/2011 Medical Policy Implementation Committee approval. No change to coverage.
05/03/2012 Medical Policy Committee review
05/16/2012 Medical Policy Implementation Committee approval. Added new drug Veletri to policy.
05/02/2013 Medical Policy Committee review
05/22/2013 Medical Policy Implementation Committee approval. Deleted the routes and NYHA Classes of each drug. Deleted the Note regarding the 3 steps of treating with epoprostenol. Deleted the Note regarding treatment with iloprost requiring the use of a specialized dispensing device. Added the brand names of each drug.
04/03/2014 Medical Policy Committee review
04/23/2014 Medical Policy Implementation Committee approval. Changed title from “Treatment of Pulmonary Arterial Hypertension with Prostacyclin Analogues, Endothelin Receptor Antagonists or Phosphodiesterase Inhibitors” to “Advanced Therapies for Treatment of Pulmonary Hypertension” due to one of the drugs being approved for WHO Group 4. Added the drugs Adempas, Opsumit, and Orenitram to the policy along with their respective indications. Updated background and rationale info with latest data from the association.
06/25/2015 Medical Policy Committee review
07/15/2015 Medical Policy Implementation Committee approval. No change to coverage.
06/02/2016 Medical Policy Committee review
06/20/2016 Medical Policy Implementation Committee approval. Added a new drug, Uptravi, to the policy. Updated background info to include Uptravi. Updated rationale and references.

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01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017 Medical Policy Committee review
06/21/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/07/2018 Medical Policy Committee review
06/20/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/10/2019 Medical Policy Committee review
01/23/2019 Medical Policy Implementation Committee approval. Revatio tablets and Adcirca are generic. Requirement to try generic product before brand was added.

Next Scheduled Review Date: 01/2020

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   A. In accordance with nationally accepted standards of medical practice;
   B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
   C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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