

Advanced Therapies for Pharmacological Treatment of Pulmonary Hypertension

Policy # 00215

Original Effective Date: 06/17/2009

Current Effective Date: 04/01/2025

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 brand and generic 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[®])[‡]
 - Note that a trial and failure (e.g., intolerance or inadequate response) of generic treprostinil INJECTION for the treatment of PAH will be required prior to the use of brand Remodulin unless there is clinical evidence or patient history that suggests the use of generic treprostinil INJECTION for the treatment of PAH will be ineffective or cause an adverse reaction to the member.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- treprostinil sodium (Tyvaso[®])[‡]
- iloprost (Ventavis[®])[‡]
- treprostinil sodium (Orenitram[®])[‡]
- treprostinil sodium (Tyvaso DPI[™])[‡]

Prostacycline Receptor Agonists

- selexipag (Uptravi[®])[‡]

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Endothelin Receptor Antagonists

- bosentan (Tracleer[®])[‡]
 - TABLETS (NON-SUSPENSION): Note that a trial and failure (e.g., intolerance or inadequate response) of generic bosentan TABLETS (NON-SUSPENSION) for the treatment of PAH will be required prior to the use of brand Tracleer TABLETS (NON-SUSPENSION) unless there is clinical evidence or patient history that suggests the use of generic bosentan TABLETS (NON-SUSPENSION) for the treatment of PAH will be ineffective or cause an adverse reaction to the member.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
 - TABLETS FOR SUSPENSION: Note that a trial and failure (e.g., intolerance or inadequate response) of generic bosentan TABLETS (NON-SUSPENSION) for the treatment of PAH will be required prior to the use of brand Tracleer TABLETS FOR SUSPENSION unless there is clinical evidence or patient history that suggests the use of generic bosentan TABLETS (NON-SUSPENSION) for the treatment of PAH will be ineffective or cause an adverse reaction to the member.
 - Examples of clinical evidence include:
 - ❖ Patient requires a dosage that can ONLY be met with TABLETS FOR SUSPENSION dosage form; OR
 - ❖ Patient has a gastrostomy tube [G-tube]; OR
 - ❖ Patient is unable to swallow tablet and or capsules AND is NOT taking any other medications in tablet and/or capsule form.*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- ambrisentan (Letairis[®])[‡]
 - Note that a trial and failure (e.g., intolerance or inadequate response) of generic ambrisentan for the treatment of PAH will be required prior to the use of brand Letairis unless there is clinical evidence or patient history that suggests the use of generic ambrisentan for the treatment of PAH will be ineffective or cause an adverse reaction to the member.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- 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.



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

- Note that a trial and failure (e.g., intolerance or inadequate response) of generic sildenafil SUSPENSION for the treatment of PAH will be required prior to the use of brand Revatio SUSPENSION unless there is clinical evidence or patient history that suggests the use of generic sildenafil SUSPENSION for the treatment of PAH will be ineffective or cause an adverse reaction to the member.

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

- tadalafil (Adcirca[®])[‡]
 - Note that a trial and failure (e.g., intolerance or inadequate response) of generic tadalafil or Alyq 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 or Alyq for the treatment of PAH will be ineffective or cause an adverse reaction to the member.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- tadalafil (Tadliq[®])[‡]
 - Patient has a gastrostomy tube (G-tube) or is otherwise unable to swallow tablets and/or capsules; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
 - Patient is NOT currently taking other medications in tablet or capsule form.
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).*
- sildenafil citrate (Liqrev[®])[‡]
 - Note that a trial and failure (e.g., intolerance or inadequate response) of generic sildenafil SUSPENSION for the treatment of PAH will be required prior to the use of brand Liqrev SUSPENSION unless there is clinical evidence or patient history that suggests the use of generic sildenafil SUSPENSION for the treatment of PAH will be ineffective or cause an adverse reaction to the member.
*(Note: This specific patient selection 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[®])[‡]

Activin Signaling Inhibitor

- sotatercept-csrk (Winrevair[™])[‡]



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Endothelin Receptor Antagonist/Phosphodiesterase 5 Inhibitor

- macitentan/tadalafil (Opsynvi[®])[‡]

Pulmonary Hypertension Associated with Interstitial Lung Disease (WHO Group 3)

Based on review of available data, the Company may consider treprostinil sodium (Tyvaso) and treprostinil sodium (Tyvaso DPI) for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD), World Health Organization (WHO) Group 3, to be **eligible for coverage****:

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) after surgical treatment OR inoperable CTEPH, World Health Organization (WHO) Group 4, 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 Remodulin when the patient has NOT tried and failed generic treprostinil INJECTION to be **not medically necessary.****

Based on review of available data, the Company considers the use of brand Tracleer TABLETS (NON-SUSPENSION) when the patient has NOT tried and failed generic bosentan TABLETS (NON-SUSPENSION) to be **not medically necessary.****

Based on review of available data, the Company considers the use of brand Tracleer TABLETS FOR SUSPENSION when the patient has NOT tried and failed generic bosentan TABLETS (NON-SUSPENSION), unless clinical evidence is provided to the contrary, to be **not medically necessary.****

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



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

Based on review of available data, the Company considers the use of Tadiq WITHOUT documentation that the patient has a gastrostomy tube (G-tube) or is otherwise unable to swallow tablets and/or capsules AND WITHOUT documentation that the patient is NOT currently taking other medications in tablet or capsule form 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/Orenitram), iloprost (Ventavis), bosentan (Tracleer), ambrisentan (Letairis), macitentan (Opsumit), sildenafil citrate (Revatio/Liqrev), selexipag (Uptravi), tadalafil (Adcirca/Tadiq), sotatercept-csrk (Winrevair), or macitentan/tadalafil (Opsynvi) 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)

Based on review of available data, the Company considers the use of treprostinil (Tyvaso/Tyvaso DPI) for the treatment of PH due to left heart disease, PH due to chronic thrombotic and/or embolic disease, and PH due to mixed or uncertain causes (WHO Groups 2, 4, and 5) to be **investigational**.*

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**.*



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Background/Overview

Pulmonary Hypertension

Classification

The 2019 WHO classification of PH, which is based on the consensus of an international group of experts at the 6th 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 medical policy (WHO groups 1, 3, and 4).

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The WHO further classifies patients with pulmonary hypertension based on functional ability:

- Class I: No limitations with ordinary physical activity
- Class II: Ordinary physical activity results in symptoms. Comfortable at rest.
- Class III: Less than ordinary physical activity results in symptoms. Comfortable at rest.
- Class IV: Inability to perform any physical activity without symptoms. Symptoms present at rest.

While PH can be diagnosed at any age, including children, the incidence of disease increases with age. Generally, PH is more common in people 75 years of age or older, as well as in women and non-Hispanic Black people. According to a 2017 statement from the American Thoracic Society (ATS), the impact of health disparities on the diagnosis, treatment, and clinical outcome of patients with PAH has not been systematically investigated. However, lower socioeconomic status, particularly lower income, has been associated with worse functional class and more advanced PAH at presentation.

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 3 (Pulmonary Hypertension due to Chronic Lung Disease and/or Hypoxemia)

PH can develop from chronic lung disease and/or hypoxia. These lung diseases include obstructive lung diseases, such as COPD or emphysema, where the lung airways are narrow making it harder to exhale and restrictive lung diseases, such as interstitial lung disease or pulmonary fibrosis, where the lungs have trouble expanding during inhalation. PH-ILD can also be due to sleep apnea and living in areas of high altitude for extended periods of time. Estimation of prevalence of individuals with this form of PH is difficult to ascertain due to the difference in type and severity of underlying disease; however, PH due to chronic lung disease and/or hypoxemia is more common in older adults. This type of PH is typically progressive and associated with increased morbidity and mortality.

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.



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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, 3, 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.
- Activin signaling inhibitor: Activin signaling inhibitors improve the balance between the pro-proliferative and anti-proliferative signaling to modulate vascular proliferation.

WHO Group 3 (Pulmonary Hypertension due to Chronic Lung Disease and/or Hypoxemia)

Tyvaso and Tyvaso DPI are currently the only agents FDA-approved for PH-ILD. The active ingredient, treprostinil sodium, is a prostacyclin analogue. These medications are administered by inhalation and help to improve ability to exercise through vasodilation.



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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), PH-ILD (WHO group 3), and CTEPH (WHO group 4) and their current regulatory status (see below Table 1 for functional class descriptions).

Drug (Brand Name) Manufacturer FDA Approval Date	Route(s) of Administration Dose Range	FDA-Approved Indications
Prostacyclin analog		
Epoprostenol sodium (Flolan) GlaxoSmithKline FDA approved 1995	<ul style="list-style-type: none"> • Continuous intravenous infusion via central venous catheter using an ambulatory infusion pump • 1-20 ng/kg/min 	<ul style="list-style-type: none"> • 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%).
Treprostinil sodium (Remodulin) United Therapeutics FDA approved 2002	<ul style="list-style-type: none"> • Continuous SC infusion • Intravenous infusion (if SC infusion not tolerated) • 0.625-1.25 ng/kg/min 	<ul style="list-style-type: none"> • 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
Treprostinil (Tyvaso, Tyvaso DPI) United Therapeutics FDA approved 2009	<ul style="list-style-type: none"> • Inhalation via DPI or nebulizer; specific to 1 pulmonary drug 	<ul style="list-style-type: none"> • Treatment of PAH (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA functional class III symptom and etiologies

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	<p>each delivery system</p> <ul style="list-style-type: none"> • Nebulizer: 18-54 µg, 4 times daily • DPI: 16-64 µg, 4 times daily 	<p>of idiopathic or heritable PAH (56%) or PAH associated with CTD (33%).</p> <ul style="list-style-type: none"> • Treatment of PH associated with interstitial lung disease (WHO group 3) to improve exercise ability. The study establishing effectiveness predominantly included patients with etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO group 3 connective tissue disease (22%).
<p>Treprostinil (Orenitram) United Therapeutics FDA approved 2013</p>	<ul style="list-style-type: none"> • Oral • Maximum dose as tolerated: 3.4-21 mg twice daily^a 	<ul style="list-style-type: none"> • 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%).
<p>Iloprost (Ventavis) Actelion Pharmaceuticals FDA approved 2004</p>	<ul style="list-style-type: none"> • Inhalation via nebulizer using a specific pulmonary drug delivery system • 2.5-5 µg, 6-9 times daily 	<ul style="list-style-type: none"> • 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%).
<p>Beraprost NOT APPROVED IN U.S. & E.U. Failed reviews Approved in Japan for treating PAH</p> <p>Prostacyclin receptor agonists</p>	<ul style="list-style-type: none"> • Oral 	<ul style="list-style-type: none"> • No FDA-approved indications for PAH
<p>Selexipag (Uptravi) Actelion Pharmaceuticals FDA approved 2015</p>	<ul style="list-style-type: none"> • Oral • Starting dose 200 mcg twice daily. Increase by 200 mcg 	<ul style="list-style-type: none"> • Treatment of PAH (WHO Group 1) to delay disease progression and reduce risk of hospitalization for PAH. Study establishing effectiveness had long term



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twice weekly to maximum dose as tolerated up to 1600 mcg twice daily.- follow up and included patients with WHO functional class II-III symptoms.

Endothelin receptor antagonists

Bosentan (Tracleer)
Actelion Pharmaceuticals
FDA approved 2001

- Oral
- 62.5-125 mg 2 times daily
- Age and weight based dosing for pediatrics.

- 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%).
- Treatment of patients 3 years of age and older with idiopathic or congenital PAH.

Ambrisentan (Letairis)
Gilead Sciences
FDA approved 2007

- Oral
- 5-10 mg daily

- Treatment of PAH (WHO group 1) to improve exercise ability and delay clinical worsening and in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness predominantly included patients with NYHA class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with CTD (34%).

Macitentan (Opsumit)
Actelion Pharmaceuticals
FDA approved 2013

- Oral
- 10 mg daily

- 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.



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Phosphodiesterase inhibitors

Sildenafil citrate (Revatio) Pfizer Labs FDA approved 2005	<ul style="list-style-type: none"> • Oral • 20 mg 3 times daily 	<ul style="list-style-type: none"> • 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.)
Tadalafil (Adcirca) Eli Lilly FDA approved 2009	<ul style="list-style-type: none"> • Oral • 40 mg once daily 	<ul style="list-style-type: none"> • 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%).
Tadalafil (Tadliq) CMP Pharma, Inc. FDA approved 2022	<ul style="list-style-type: none"> • Oral • 40 mg once daily 	<ul style="list-style-type: none"> • Treatment of PAH (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).
Vardenafil (Levitra) Bayer Healthcare FDA approved (but not for PAH)	<ul style="list-style-type: none"> • Oral 	<ul style="list-style-type: none"> • No FDA-approved indications for PAH. One randomized trial outside of United States
Sildenafil (Liqrev) CMP Pharma FDA approved 2023	<ul style="list-style-type: none"> • Oral • 20 mg 3 times daily 	<ul style="list-style-type: none"> • Treatment of PAH (WHO Group 1) in adults to improve exercise ability and delay clinical worsening
Activin signaling inhibitor		
Sotatercept-csrk (Winrevair) Merck FDA approved 2024	<ul style="list-style-type: none"> • Subcutaneous injection 	<ul style="list-style-type: none"> • Treatment of PAH (WHO Group 1) to increase exercise capacity, improve WHO



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	<ul style="list-style-type: none"> • Starting dose 0.3 mg/kg every 3 weeks • Target dose 0.7 mg/kg every 3 weeks 	functional class (FC) and reduce the risk of clinical worsening events
Endothelin receptor antagonist/Phosphodiesterase 5 inhibitor Combination		
Macitentan/Tadalafil (Opsynvi) Actelion Pharmaceuticals FDA approved 2024	<ul style="list-style-type: none"> • Oral • 10 mg/20 mg or 10 mg/40 mg once daily 	<ul style="list-style-type: none"> • Chronic treatment of PAH (WHO Group 1) in adult patients of WHO functional class (FC) II-III • Macitentan reduces the risk of clinical worsening events and hospitalization • Tadalafil improves exercise ability
Soluble guanylate cyclase stimulator		
Riociguat (Adempas) Bayer HealthCare FDA approved 2013	<ul style="list-style-type: none"> • Oral • 0.5-2.5 mg 3 times daily 	<ul style="list-style-type: none"> • 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
Tyrosine kinase inhibitors		
Imatinib (Gleevec®)† Novartis FDA approved (but not for PAH)	<ul style="list-style-type: none"> • Oral 	<ul style="list-style-type: none"> • No FDA-approved indications for PAH. Two randomized trials as add-on medication.
Statins		
Simvastatin FDA approved (but not for PAH)	<ul style="list-style-type: none"> • Oral 	<ul style="list-style-type: none"> • No FDA-approved indications for PAH. One randomized trial with and without aspirin showed no effect on exercise ability.
Atorvastatin FDA approved (but not for PAH)	<ul style="list-style-type: none"> • Oral 	<ul style="list-style-type: none"> • No FDA-approved indications for PAH. One randomized trial showed no clinical benefit compared with placebo.



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CTD: connective tissue diseases; CTEPH: chronic thromboembolic pulmonary hypertension; DPI: dry powder inhaler; FDA: U.S. Food and Drug Administration; PAH: pulmonary arterial hypertension; SC: subcutaneous; NYHA: New York Heart Association; WHO: World Health Organization.

^a 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	
Class I	Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Patients with slight, mild limitation of activity; they are comfortable with rest or mild exertion.
Class III	Patients with marked limitation of activity; they are comfortable only at rest.
Class IV	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.
World Health Organization (WHO) - functional classification for pulmonary arterial hypertension (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, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The most recent literature review for this policy was performed through October 9, 2023. 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), PH due to chronic lung disease and/or hypoxemia (WHO group 3), and CTEPH (WHO group 4). Some off-label treatments also are discussed for these 2 indications.



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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

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

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 [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.”



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Section Summary: PAH Monotherapy Using Tyrosine Kinase Inhibitors or Statins

There are no RCTs evaluating the efficacy of tyrosine kinase inhibitors for PAH and 4 RCTs on statins for PAH. A meta-analysis of RCTs evaluating statins for PAH did not report significantly better outcomes (i.e., mortality, 6MWD) with the study medication than with placebo. For imatinib, a tyrosine kinase inhibitor, there are no placebo-controlled studies evaluating efficacy. However, a 2016 safety study identified a high rate of adverse 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

Study	Study Eligibility and No. Included Studies	Summary of Results
Lajoie et al (2016)	<ul style="list-style-type: none"> • RCTs of PAH-specific combination therapy vs monotherapy in adults; ≥12 wk in duration • 17 studies 	All-cause mortality: <ul style="list-style-type: none"> • RR=0.88 (95% CI, 0.74 to 1.05) (16 studies) Clinical worsening ^a : <ul style="list-style-type: none"> • RR=0.65 (95% CI, 0.56 to 0.76) (15 studies) Hospitalization: <ul style="list-style-type: none"> • RR=0.71 (95% CI, 0.53 to 0.96) (8 studies)
McCrory et al (AHRQ) (2013)	<ul style="list-style-type: none"> • RCTs of PAH-specific combination therapy vs monotherapy • 5 studies 	All-cause mortality: <ul style="list-style-type: none"> • OR=0.37 (95% CI, 0.04 to 3.32) (3 studies) 6MWD (m): <ul style="list-style-type: none"> • MD=23.9 (95% CI, 8.0 to 39.9) Hospitalization: <ul style="list-style-type: none"> • OR=0.64 (95% CI, 0.31 to 1.36) (3 studies)
Fox et al (2011)	<ul style="list-style-type: none"> • RCTs PAH-specific combination therapy 	All-cause mortality: <ul style="list-style-type: none"> • RR=0.42 (95% CI, 0.08 to 2.26) (4 studies) Clinical worsening ^a :



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vs monotherapy; ≥ 12 wk in duration
• 6 studies

• 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.

^aClinical 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 (McCorry 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 Dual Therapies

Two RCTs specifically evaluating initial combination therapy in patients with PAH were identified. A 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



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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).

The Bosentan Randomized trial of Endothelin Antagonist Therapy for PAH (BREATHE-2) trial, reported by Humbert et al in 2004 compared epoprostenol alone with the combination of epoprostenol plus bosentan. The trial was multicenter, double-blind, and placebo-controlled. It included 33 patients with PAH who were scheduled to begin treatment with epoprostenol. After 2 days of epoprostenol therapy, patients were randomized to add bosentan ($n = 22$) or placebo ($n = 11$). The double-blind treatment duration was 16 weeks, and the primary efficacy outcome was change in total pulmonary resistance. Five (15%) of 33 patients did not complete the trial. At 16 weeks, mean change in total pulmonary resistance did not differ significantly between groups ($-36.3 \text{ dyns}^{-1} \text{cm}^5 \pm 4.3\%$ in the combination treatment group vs. $-22.6 \text{ dyns}^{-1} \text{cm}^5 \pm 4.3\%$ in the epoprostenol plus placebo group, $p = .08$). Secondary outcomes also did not differ significantly between groups. For example, the median 6MWD increased 68 meters in the combination treatment group and 74 meters in the epoprostenol plus placebo group. Moreover, the modified New York Heart Association functional class improved for 59% (13 of 22) of patients in the combination treatment group and 45% (5 of 11) of patients in the epoprostenol plus placebo group, a difference that was not statistically significant.

A retrospective study evaluated the long-term survival of patients with idiopathic, heritable, or anorexigen-induced PAH categorized according to the initial treatment strategy (monotherapy, dual therapy, or triple-combination therapy). Data were abstracted from the French Pulmonary Hypertension Registry (January 2006 to December 2018) and included 984 patients initiated on monotherapy, 551 initiated on dual therapy, and 76 initiated on triple therapy. The 5-year survival rate for patients who were initiated on dual therapy or monotherapy was 61% for both groups; similarly, the 10-year survival rate for patients initiated on dual therapy or monotherapy was 43% for both groups.

Section Summary: PAH Therapy Using Combination Initial Dual Therapies

Two RCTs have compared 6 months of initial combination therapy versus monotherapy for PAH. A long-term retrospective study comparing overall survival between treatments was also published. In the AMBITION trial, 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. The other RCT did not find significant differences in outcomes between a group receiving initial combined therapy and a group receiving monotherapy at 16 weeks; this study had a



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small sample size and might have been underpowered for secondary outcomes. These 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. A retrospective study found similar 5- and 10-year overall survival for patients initiated on dual therapy or monotherapy.

Pulmonary Arterial Hypertension Therapy Using Combination Initial Triple Therapies

One RCT specifically evaluating initial triple combination therapy in patients with PAH was identified. The Efficacy and Safety of Initial Triple Versus Initial Dual Oral Combination Therapy in Patients With Newly Diagnosed Pulmonary Arterial Hypertension (TRITON) was a multicenter, double-blind, RCT comparing initial triple therapy (n=123) with macitentan, tadalafil, and selexipag to initial double therapy (n=124) with macitentan, tadalafil, and placebo in newly diagnosed, treatment-naive patients with PAH. At baseline, approximately 80% of patients had WHO functional class II or III symptoms. At week 26, the primary endpoint of change in PVR was reduced by 54% and 52% with initial triple and dual therapy, respectively, but the between-group difference was not significant. Secondary endpoints were considered exploratory based on testing hierarchy, and potentially signaled a reduced risk for disease progression events with initial triple therapy (rate ratio, 0.39; 95% CI, 0.15 to 1.00). Overall, larger studies powered to find long-term benefits with triple therapy are needed to identify patients who may benefit from this treatment approach.

Section Summary: PAH Therapy Using Combination Initial Triple Therapies

For individuals who have PAH who receive initial combination therapy using 3 drug classes FDA approved for treatment of PAH, the evidence includes 1 RCT. In the TRITON trial, initial triple therapy was compared to initial double therapy in newly diagnosed, treatment-naive patients with PAH, most of whom had WHO functional class II or III symptoms. At week 26, the primary endpoint of change in PVR was reduced by 54% and 52% with initial triple and dual therapy, respectively, but the between-group difference was not significant. The frequency of serious adverse events was similar in both groups. Overall, larger studies powered to find long-term benefits with triple therapy are needed to identify patients who may benefit from this treatment approach.

Inoperable 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%



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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.

Additional data on secondary outcomes from CHEST-1 were published by Kim et al (2017). Study findings generally favored the riociguat group. At week 16, compared with baseline, PVR significantly decreased in the riociguat group (-29%) compared with the placebo group (+3%). There were also significantly improved outcomes in the riociguat group versus placebo for other hemodynamic outcomes (eg, systemic vascular resistance, mean pulmonary arterial pressure, diastolic pulmonary artery pressure, cardiac output, mixed venous oxygen saturation, mean arterial pressure, diastolic pressure gradient; $p < .001$ for each).

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.

Riociguat Versus Balloon Pulmonary Angioplasty in Non-operable Chronic thromboembolic Pulmonary Hypertension (RACE) was a RCT that compared the efficacy and safety of balloon pulmonary angioplasty (BPA) versus riociguat in patients with inoperable CTEPH. In this open-label trial done in 23 French PAH centers, treatment-naïve adults with newly diagnosed, inoperable CTEPH and PVR of more than $320 \text{ dyns}^{-1} \text{cm}^5$ were randomized to receive riociguat 1 to 2.5 mg 3 times daily ($n=53$) or BPA ($n=52$). At week 26, the geometric mean PVR decreased to 39.9% (95% CI, 36.2 to 44) of baseline PVR in the BPA group and 66.7% (60.5 to 73.5) of baseline PVR in the riociguat group (ratio of geometric means, 0.60; 95% CI, 0.52 to 0.69; $p < .0001$). The change in 6MWD was not significantly different between the BPA (50.3 m) and riociguat (44.1 m) group (treatment effect, 6.14 m; 95% CI, -18.12 to 30.4 m; $p=.62$). Treatment-related serious adverse events were more frequently observed in patients in the BPA (42%) versus the riociguat (9%) group.



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Patients who completed the RACE trial continued into an ancillary 26-week follow-up during which symptomatic patients with PVR of more than $320 \text{ dyns}^{-1}\text{cm}^5$ benefited from add-on riociguat after BPA or add-on BPA after riociguat. Amongst patients who completed the initial 26-week trial, criteria for add-on riociguat were met by 18 of 51 patients in the BPA group, and criteria for add-on BPA was met by 36 of 48 patients in the riociguat group. At week 52, the exploratory analysis showed that the geometric mean of PVR decreased to 35% (95% CI, 31.7 to 38.7) of the baseline value in the group who received add-on riociguat, and decreased to 38.6% (95% CI, 35 to 42.6) in the group who received add-on BPA (ratio of geometric means, 0.91; 95% CI, 0.79 to 1.04; $p=.18$).

Treprostinil

Sadushi-Kolici et al, published in 2019, conducted a 24-week, double-blind RCT assessing the efficacy and safety of treprostinil, a prostacyclin analogue, for the treatment of inoperable CTEPH. One hundred five patients were enrolled in the study, 53 randomly assigned to receive high-dose subcutaneous treprostinil (target dose approximately 30 ng/kg/min at week 12) and 52 assigned to receive a low dose (target dose approximately 3 ng/kg/min at week 12). The primary endpoint was 6MWD at week 24. At week 24, the marginal mean 6MWD in the high-dose group improved by 44.98 m (95% CI, 27.52 to 62.45 m), and the low-dose group improved by 4.29 m (95% CI, -13.34 to 21.92 m); treatment effect was 40.69 m (95% CI, 15.86 to 65.53 m; $p=.0016$). Patients in both groups (high-dose group $n=9$ [17%]; low-dose group $n=10$ [19%]) experienced serious adverse events, but the most common adverse events reported were infusion site pain and other infusion site reactions.

Section Summary: CTEPH Monotherapy

There is only 1 FDA-approved medication for this indication: riociguat. Two RCTs and their extension studies have been published. One double-blind, placebo controlled RCT 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. In the second RCT, the efficacy and safety of BPA and riociguat were compared. At week 26, PVR reduction was more pronounced with BPA than with riociguat, but treatment-related serious adverse events were more common with BPA. A 52-week extension study found that add-on BPA or add-on riociguat had similar effects on PVR reduction.

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 poprostenol for a mean of



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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.

Pulmonary Hypertension Associated with Interstitial Lung Disease Therapy

Tyvaso was evaluated in one 16 week, randomized, double-blind, placebo-controlled, multicenter study (INCREASE) that enrolled 326 patients with PH-ILD. Enrolled study patients predominately had etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%). The mean baseline 6MWD was 260 meters.



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Patients in the INCREASE study were randomized (1:1) to either placebo or Tyvaso in 4 daily treatment sessions with a target dose of 9 breaths (54 mcg) per session and a maximum dose of 12 breaths (72 mcg) per session over the course of the 16-week study. Approximately 75% of patients randomized to Tyvaso titrated up to a dose of 9 breaths, 4 times daily or greater, with 48% of patients randomized to Tyvaso reaching a dose of 12 breaths, 4 times daily during the study.

The primary efficacy endpoint was the change in 6MWD measured at peak exposure (between 10 and 60 minutes after dosing) from baseline to Week 16. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 21 meters at Week 16 ($p=0.004$) using Hodges Lehmann estimate.

Time to clinical worsening in the INCREASE study was defined as the time of randomization until 1 of the following criteria were met: hospitalization due to a cardiopulmonary indication, decrease in 6MWD $>15\%$ from baseline directly related to PH-ILD at 2 consecutive visits and at least 24 hours apart, death (all causes), or lung transplantation. Treatment with Tyvaso in patients with PH-ILD resulted in numerically fewer hospitalizations. The numbers of reported deaths were the same for both treatment groups. Overall, treatment with Tyvaso demonstrated a statistically significant increase in the time to first clinical worsening event (log-rank test $p=0.041$; Figure 5), and a 39% overall reduction in the risk of a clinical worsening event (HR=0.61 [95% CI; 0.40, 0.92]).

Section Summary: PH-ILD Therapy

There are only 2 FDA-approved medications for this indication: Tyvaso and Tyvaso DPI. The active ingredient, treprostinil, was studied in 1 RCT. In the INCREASE trial, there was significant improvement in exercise capacity in patients treated with inhaled treprostinil compared to those treated with placebo. Treatment with treprostinil was also associated with a lower risk of clinical worsening than that in patients who were treated with placebo. Adverse reactions from treprostinil therapy were similar to what was observed in studies for PAH. The number of deaths was equal across both treatment arms.

Summary of Evidence

For individuals who have PAH who receive monotherapy using TKIs or statins, the evidence includes 4 RCTs and a meta-analysis on statins and no RCTs on tyrosine kinase inhibitors. 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



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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 2 RCTs and a retrospective study. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The first RCT compared initial monotherapy and initial combination therapy. There was a significantly lower rate of clinical failure at 6 months in the combination therapy group than in the monotherapy group in this study. Clinical failure was defined as a complex composite endpoint that included death, hospitalizations, functional improvement, and other measures of disease progression. Study limitations include change in enrollment criteria during the trial and use of a complex composite outcome with multiple components. The other RCT did not find significant differences in outcomes between a group receiving initial combination therapy and the group receiving monotherapy at 16 weeks; this study had a small sample size and might have been underpowered to assess secondary outcomes. Multiple reviews of the AMBITION trial with an emphasis on functional improvement (6MWT) have led to guideline recommendations for making ambrisentan plus tadalafil and appropriate initial treatment option. A retrospective study found similar 5- and 10-year overall survival for patients initiated on dual therapy or monotherapy. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have PAH who receive initial combination therapy using 3 drug classes FDA approved for treatment of PAH, the evidence includes single RCT. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. In the trial, initial triple therapy was compared to initial double therapy in newly diagnosed, treatment-naive patients with PAH. At week 26, the primary endpoint of change in PVR was reduced by 54% and 52% with initial triple and dual therapy, respectively, but the between-group difference was not significant. Secondary endpoints were considered exploratory based on testing hierarchy, and potentially signaled a reduced risk for disease progression events with initial triple therapy. Overall, larger studies powered to find long-term benefits with triple therapy are needed to identify patients who may benefit from this treatment approach. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have CTEPH or PH after surgery who receive a soluble guanylate cyclase stimulator (e.g., riociguat), the evidence includes 2 RCTs. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. The first double-blind, placebo-controlled RCT found that functional outcomes at 16 weeks improved significantly more in



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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. In the second RCT, the efficacy and safety of balloon pulmonary angioplasty (BPA) and riociguat were compared. At week 26, PVR reduction was more pronounced with BPA than with riociguat, but treatment-related serious adverse events were more common with BPA. A 52-week extension study found that add-on BPA or add-on riociguat had similar effects on PVR reduction. 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 mortality and PVR improve with any of these medications. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have PH-ILD who receive inhaled treprostinil, the evidence includes 1 RCT. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. In the trial, there was significant improvement in exercise capacity in patients treated with inhaled treprostinil. Treatment with treprostinil was also associated with a lower risk of clinical worsening compared to the patients who were treated with placebo. The number of deaths was equal among both treatment groups. The evidence is sufficient to determine the effects of the technology on health outcomes.

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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. |



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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 information.

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, Upravi, to the policy. Updated background info to include Upravi. Updated rationale and references.

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.

11/07/2019 Medical Policy Committee review
11/13/2019 Medical Policy Implementation Committee approval. Added generic Letairis, Tracleer, and Revatio suspension to the policy. Added criteria for the Tracleer suspension.

11/05/2020 Medical Policy Committee review
11/11/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

11/04/2021 Medical Policy Committee review
11/10/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

12/01/2022 Medical Policy Committee review
12/14/2022 Medical Policy Implementation Committee approval. Added two new drugs, Tyvaso DPI and Tadliq, to the policy. Updated literature review.

11/02/2023 Medical Policy Committee review
11/08/2023 Medical Policy Implementation Committee approval. Added new drug, Liqrev, to the policy with criteria.

08/01/2024 Medical Policy Committee review



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08/14/2024 Medical Policy Implementation Committee approval. Added two new drugs to the policy, Opsynvi and Winrevair, with criteria. Updated literature review.

01/02/2025 Medical Policy Committee review

01/08/2025 Medical Policy Implementation Committee approval. Added the requirement that a patient try and fail generic treprostinil injection prior to brand Remodulin. Removed requirement that generic tadalafil and Opsumit be tried and failed prior to Opsynvi.

Next Scheduled Review Date: 01/2026

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	C9399, J1325, J3285, J3590, J7686, K0455, K0730, Q4074, S0090, S0155, S9347
ICD-10 Diagnosis	All related Diagnoses



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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.



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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

