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Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-

reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Pulmonary Arterial Hypertension (PAH)
Combination therapy for the treatment of pulmonary arterial hypertension (World Health Organization [WHO] Group 1) **may be considered medically necessary** when **ALL** of the following conditions are met:

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

Use of other advanced therapies for the pharmacologic treatment of PAH (WHO Group 1) that are not approved by the U.S. Food and Drug Administration for this indication **are considered experimental, investigational and/or unproven.**

Pulmonary Hypertension
The use of epoprostenol and treprostinil **is considered experimental, investigational and/or unproven** for the treatment of pulmonary hypertension (PH; WHO Groups 2-5), including but not limited to:

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

NOTE: For oral agents (e.g., bosentan, ambrisentan, macitentan, sildenafil, tadalafil, vardenafil, riociguat, treprostinil, selexipag) please refer to applicable pharmacy benefit plan(s).

Policy Guidelines

This medical policy addresses advanced pharmacologic therapies for pulmonary hypertension (PH). Advanced pharmacologic therapies are newer specialty pharmacy drugs specifically intended to impact the natural history of PH, rather than supportive medications that treat

disease manifestations. The drugs addressed in this medical policy are currently approved by the U.S. Food and Drug Administration (FDA) only for a subset of classes of PH (Groups 1 and 4); as a result, the policy will only address classes of PH for which advanced pharmacologic therapies are approved. For oral agents please refer to applicable pharmacy benefit plan(s).

Description

Pulmonary Hypertension

Classification

The 2019 World Health Organization (WHO) classification of PH, which is based on the consensus of an international group of experts at the Sixth World Symposium on Pulmonary Hypertension, is the most widely used system used in clinical care and research. (1) There are 5 WHO categories of PH based on the etiology of the pulmonary hypertension:

- Group 1: Pulmonary arterial hypertension (PAH).
- Group 2: Pulmonary hypertension due to left heart disease.
- Group 3: Pulmonary hypertension due to chronic lung disease and/or hypoxemia.
- Group 4: Pulmonary hypertension due to chronic thromboembolic disease (chronic thromboembolic pulmonary hypertension [CTEPH]).
- Group 5: Pulmonary hypertension due to mixed or uncertain causes.

For each category, 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

Pulmonary hypertension (PH) is defined as increased arterial pressure in the lung vasculature. (2) Increased pulmonary pressure can be caused by primary abnormalities in the pulmonary vascular system; it can also be caused by other abnormalities in the cardiac or pulmonary organs, which may lead to secondary elevations in pulmonary arterial pressure. A definitive diagnosis of PH is usually made following measurement of pulmonary arterial pressure by right heart catheterization. A pulmonary arterial pressure of at least 20 mm mercury (Hg) confirms the diagnosis. (1, 3)

Clinical symptoms of PH are related to right-sided heart failure and impaired oxygen delivery by the lungs. Warning signs are nonspecific, but often present as a constellation of symptoms including dyspnea on exertion, fatigue, weakness, and syncope. (4) High pulmonary pressures lead to increased work of the right ventricle. This chronic hemodynamic overload leads to low cardiac output and progressive right ventricular dilatation. In advanced disease, signs of right-sided heart failure occur (e.g., abdominal distension, hepatic congestion, pedal edema).

Without treatment, the disease is progressive and eventually fatal; however, the natural history and rapidity of progression is variable. Premature death most commonly results from complications of right heart failure.

There are also differences in the pathophysiology, clinical manifestations, and natural history of each PH category. Only categories relevant to this medical policy (WHO Groups 1 [PAH] and 4 [CTEPH]) are discussed herein.

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. (5) 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. (6) However, lower socioeconomic status, particularly lower income, has been associated with worse functional class and more advanced PAH at presentation.

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 both anticoagulation and surgical thrombectomy are treatment options for appropriate patients in group 4. (3)

Advanced Pharmacologic Therapies

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

WHO Group 1 (Pulmonary Arterial Hypertension)

Table 1 lists the classes of medications with FDA approvals for treatment of PAH.

Table 1. Approved Medication Classes for Treating Pulmonary Arterial Hypertension

Class	Definition
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.
PDE inhibitors	PDE inhibitors are cyclic guanosine monophosphate inhibitors. Cyclic guanosine monophosphate inhibition results in reduced breakdown and longer duration of nitric oxide, which is a potent vasodilator.
Soluble guanylate cyclase stimulator	Riociguat is a first-in-class oral soluble guanylate cyclase stimulator.

IP: prostacycline receptor, also known as the prostaglandin I2 receptor or IP; PDE: phosphosdiesterase.

Regulatory Status

Table 2 summarizes advanced therapies for treatment of PAH (WHO Group 1) and their current regulatory status.

Table 2. Regulatory Status of Advanced Treatments of PAH

Drug (Brand) Name Manufacturer FDA Approval Date	Routes of Administration Dose Range	FDA-Approved Indications
Prostacyclin analogue (i.e., prostanoids)		
Epoprostenol sodium (Flolan®) GlaxoSmithKline 1995	• Continuous IV infusion via central venous catheter using an ambulatory infusion pump. • 1-20 ng/kg/min.	• Treatment of PAH (WHO group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly (97%) patients with NYHA class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with CTD (51%).
Epoprostenol sodium (Veletri®) Actelion Pharmaceuticals 1995	• Continuous IV infusion via central venous catheter using an ambulatory infusion pump. • 1-20 ng/kg/min.	• Treatment of PAH (WHO group 1) to improve exercise capacity. Studies establishing effectiveness included predominately patients with NYHA class III-IV symptoms and etiologies of

		idiopathic or heritable PAH or PAH associated with CTD.
Treprostinil sodium (Remodulin®) United Therapeutics 2002	• Continuous SC infusion. • IV infusion (if SC infusion not tolerated). • 0.625-1.25 ng/kg/min.	• Treatment of PAH (WHO group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with CTD (19%). • Patients who require transition from epoprostenol sodium (Flolan), to reduce rate of clinical deterioration.
Treprostinil (Tyvaso®, Tyvaso® DPI) United Therapeutics 2009	• Inhalation via DPI or nebulizer; specific to 1 pulmonary drug delivery system. • Nebulizer: 18-54 µg, 4 times daily. • DPI: 16-65 µg, 4 times daily.	• Treatment of PAH (WHO group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with CTD (33%). • Treatment of PH associated with interstitial lung disease (WHO group 3) to improve exercise ability. The study established effectiveness predominately 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%).
Treprostinil (Orenitram®) United Therapeutics 2013	• Oral. • Maximum dose as tolerated: 3.4-21 mg twice daily.[a]	• Treatment of PAH (WHO group 1) to delay disease progression and to improve exercise capacity. The studies that established effectiveness included predominately patients with WHO functional class II-III symptoms

		and etiologies of idiopathic or heritable PAH (66%) or PAH associated with CTD (26%).
Iloprost (Ventavis®) Actelion Pharmaceuticals 2004	• Inhalation via nebulizer using a specific pulmonary drug delivery system. • 2.5-5 µg, 6-9 times daily.	• Treatment of PAH (WHO group 1) to improve a composite end point consisting of exercise tolerance, symptoms (NYHA class), and lack of deterioration. Studies establishing effectiveness predominately included patients with NYHA class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with CTD (23%).
Beraprost NOT APPROVED IN U.S. AND E.U. Failed reviews Approved in Japan for PAH	• Oral.	• No FDA-approved indications.
Prostacyclin receptor agonists		

Selexipag (Uptravi®) Actelion Pharmaceuticals 2015	• Oral.
	  ○ Starting dose 200 µg twice daily. Increase by 200 µg twice weekly to maximum tolerated dose up to 1600 µg twice daily.
	• IV infusion (for patients temporarily unable to take oral therapy)
	  ○ 225 to 1800 µg twice daily.
		• Treatment of PAH (WHO group 1) to delay disease progression and reduce risk of hospitalization for PAH. Study establishing effectiveness had long-term follow-up and included patients with WHO functional class II-III symptoms.

Endothelin receptor antagonists		
Bosentan (Tracleer®) Actelion Pharmaceuticals 2001	• Oral. ○ 62.5-125 mg twice daily.	• Treatment of PAH (WHO group 1) to improve exercise ability and decrease clinical worsening. Studies establishing effectiveness predominantly included patients with NYHA class II-IV symptoms and etiologies of idiopathic

		or heritable PAH (60%), PAH associated with CTD (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%).
Ambrisentan (Letairis®) Gilead Sciences 2007	• Oral. o 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 2013	• Oral. o 10 mg daily.	• Treatment of PAH (WHO group 1) to delay disease progression (defined as death, initiation of IV or SC prostanoids, or clinical worsening of PAH [decreased 6-minute walk distance, worsened PAH symptoms, need for additional PAH treatment]). Macitentan also reduced hospitalization for PAH.
Phosphodiesterase inhibitors		
Sildenafil citrate (Revatio®) Pfizer Labs 2005	• Oral. o 20 mg 3 times daily. • IV bolus injection o 10 mg 3 times daily.	• 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%). • Treatment of PAH (WHO Group 1) in pediatric patients 1 to 17 years old to improve exercise ability and, in patients too young to perform standardized exercise testing,

		pulmonary hemodynamics thought to underly improvements in exercise.
Tadalafil (Adcirca®) Eli Lilly 2009	• Oral. ○ 40 mg once daily.	• Treatment of PAH (WHO group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA class II-III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with CTD (23%).
Vardenafil (Levitra®) 2003	• Oral.	No FDA-approved indications for PAH.
Soluble guanylate cyclase stimulator		
Riociguat (Adempas®) Bayer HealthCare 2013	• Oral. ○ 0.5-2.5 mg 3 times daily.	• Treatment of adults with PAH (WHO group 1) to improve exercise capacity and WHO functional class and to delay clinical worsening.
Tyrosine kinase inhibitors		
Imatinib (Gleevec®) 2001	• Oral.	• No FDA-approved indications for PAH.
Statins		
Simvastatin 1991	• Oral.	• No FDA-approved indications for PAH.
Atorvastatin 1999	• Oral.	• No FDA-approved indications for PAH.

CTD: connective tissue disease; E.U.: European Union; DPI: dry powder inhaler; FDA: Food and Drug Administration; PAH: pulmonary arterial hypertension; NYHA: New York Heart Association; SC: subcutaneous; U.S.: United States; WHO: World Health Organization; wk: week; IV: intravenous.
[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.

Rationale

This medical policy was originally created in August 2003 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 9, 2023.

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

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

Pulmonary Arterial Hypertension Monotherapy Using Tyrosine Kinase Inhibitors or Statins

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with PAH. PAH is characterized pathophysiologically by abnormal proliferation of pulmonary artery smooth muscle cells in the arteries. (2) This causes a decrease in the size of the pulmonary artery lumen, decreased reactivity of the vascular bed, increased pulmonary vascular resistance, and elevated pressure in the pulmonary circulation. Idiopathic PAH is the most common type of PAH and is more prevalent in women than in men. It often affects women in the third or fourth decade, resulting in a very high burden of illness for young, otherwise healthy patients. Median 1-year survival has been estimated to be 85%, and median 5-year survival has been estimated to be 57%. (7)

Interventions

The therapy being considered is monotherapy using TKIs or statins.

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

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

Outcomes
The general outcomes of interest are overall survival, functional outcomes (such as 6-minute walking distance), hospitalizations, and treatment-related morbidity. Follow-up ranges from months to years to monitor outcomes.

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

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

Tyrosine Kinase Inhibitors
No RCTs were identified that evaluated imatinib as monotherapy for patients with PAH. The safety of imatinib in patients with PAH was assessed by Frost et al. (2015) in a long-term extension of an RCT of imatinib as add-on third-line therapy. (8) A total of 144 patients entered the extension study (66 who had been on imatinib for 24 weeks, 78 were switching to imatinib from placebo). One hundred thirty-five (94%) of 144 patients discontinued the extension study and about one-third discontinued because of adverse events. When the study was terminated (due to high dropout rate), the mean exposure to imatinib was 931 days in the group who took imatinib in the original RCT and 590 days in the ex-placebo group. Seventeen (12%) of the 144 patients died during the study or within 30 days of leaving it. Serious adverse events (other than death) occurred in 40 (60.6%) patients in the group originally taking imatinib and 53 (67.9%) in the ex-placebo group. The trialists concluded that imatinib should not be used off-label for treatment of PAH.

Statins
Anand et al. (2016) published a systematic review of placebo-controlled RCTs evaluating statins for treating PAH. (9) Reviewers identified 4 RCTs, of which two evaluated simvastatin, one assessed atorvastatin, and one evaluated rosuvastatin. The total sample size was 387; 1 study had 220 patients and the others had fewer than 100 patients each. The primary outcomes of the review were mortality and change in 6-minute walk distance (6MWD) from baseline to follow-up. A pooled analysis of data from 3 trials did not find a significant benefit of stains on mortality (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.32 to 1.74; I^2=0%). Similarly, a pooled analysis of 3 trials did not find a significant benefit of statins on the 6MWD (weighted mean difference [WMD], -9.27 meters; 95% CI, -27.7 to 9.2 meters; I^2=1.7%).

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

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

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

Pulmonary Arterial Hypertension (PAH) Therapy Treated with Add-On Combination Therapies

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this policy.

Populations

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

Interventions

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

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Systematic Reviews

Meta-analyses have considered various combinations of medications; all of the individual trials included in the meta-analyses used medications from different classes. In addition, all trials used combination therapy as add-on treatment for patients with an inadequate response to a single medication. (Several trials in the Lajoie et al. [2016] (11) 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 Assessing Add-On Combination Therapy Versus Monotherapy

Study	No. of Studies	Study Eligibility	No. of Studies	Summary of Results (95% CI)
Lajoie et al. (2016) (11)	17	• RCTs of PAH-specific combination therapy vs monotherapy in adults. • ≥12 wk in duration.	16 15 8	All-cause mortality: • RR=0.88 (95% CI, 0.74 to 1.05) Clinical worsening[a]: • RR=0.65 (95% CI, 0.56 to 0.76) Hospitalization: • RR=0.71 (95% CI, 0.53 to 0.96).
McCrory et al. (2013) (12) (AHRQ)	5	• RCTs of PAH-specific combination therapy vs monotherapy.	3 3 3	All-cause mortality: • OR=0.37 (0.04 to 3.32) 6MWD (m): • MD=23.9 (8.0 to 39.9) Hospitalization: • OR=0.64 (0.31 to 1.36).

Fox et al. (2011) (13)	6	• RCTs PAH-specific combination therapy vs monotherapy • ≥12 wk in duration.	4 4 4	All-cause mortality: • RR=0.42 (95% CI, 0.08 to 2.26) Clinical worsening[a]: • RR=0.42 (95% CI, 0.17 to 1.04) 6MWD (m): • MD=25.2 (95% CI, 13.3. to 38.2).

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; wk: week; 6MWD: 6-minute walk distance.

[a] 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 lower rates of hospitalizations and less clinical worsening with the addition of a second class of medications compared with a single medication. Several meta-analyses found significantly greater exercise capacity, as measured by 6MWD with add-on combination therapy; however, the additional distance walked may not be clinically significant. The 2013 Agency for healthcare Research and Quality comparative effectiveness review by McCrory et al. (2013) indicated that 33 meters is generally considered the minimally important difference in distance walked in 6MWD. (12) None of the meta-analyses found significantly less all-cause mortality with add-on combination therapy.

Randomized Controlled Trials

Randomized controlled trials have evaluated various medication combinations for treating PAH. These combinations include, but are not limited to, prostacyclin analogues and endothelin receptor antagonists, (14, 15, 16) phosphodiesterase (PDE) inhibitors and endothelin receptor antagonists, (17, 18) and prostacyclin analogues and PDE inhibitors. (14, 19) A RCT evaluating riociguat plus sildenafil (PDE type 5 [PDE5] inhibitors) concluded that this combination is contraindicated. (20) These RCTs are included in the meta-analyses described above and will not be comprehensively summarized herein. Below is a summary of subsequently published RCTs with notable characteristics.

In the FREEDOM-EV trial, 690 patients with Group I PAH were randomized to oral treprostinil or placebo add-on therapy 30 days or longer after beginning treatment with sildenafil, tadalafil, bosentan, ambrisentan, macitentan, or riociguat. The primary outcome was time to clinical worsening (death; hospitalization due to worsening PAH; initiation of inhaled or parenteral prostacyclin therapy; disease progression; or unsatisfactory long-term clinical response). (21) At follow-up of 24 weeks, clinical worsening occurred in 26% of the oral treprostinil group compared with 36% of placebo participants (hazard ratio, 0.74; 95% CI, 0.56 to 0.97; p=.028). Discontinuation due to adverse events was more common in the treprostinil–assigned participants (18.8%) than in placebo participants (4.1%). This trial was the basis for an expanded FDA indication for treprostinil to include delaying disease progression in patients with PAH.

Section Summary: Therapy Using Add-On Combination Therapies

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

Summary of Evidence

For individuals with pulmonary arterial hypertension (PAH) who receive monotherapy using tyrosine kinase inhibitors (TKIs) or statins, the evidence includes no randomized controlled trials (RCTs) on TKIs and 4 RCTS and a meta-analysis on statins. Relevant outcomes are overall survival, functional outcomes, hospitalizations, and treatment-related morbidity. A meta-analysis of RCTs evaluating statins for PAH did not find significantly better outcomes (i.e., mortality, 6-minute walk distance) with study medication than with placebo. For imatinib (a TKI), there are no placebo-controlled studies evaluating efficacy. However, a 2016 safety study identified a high rate of adverse events in patients who took imatinib. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

Practice Guidelines and Position Statements

Pulmonary Arterial Hypertension

American College of Cardiology Foundation et al.

In 2009, the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) released an expert consensus document on pulmonary hypertension (PH) developed with 3 other medical associations. (2) This evidenced-based treatment algorithm stated that “in general, patients with poor prognostic indexes should be initiated on parenteral therapy, while

patients with class II or early II symptoms commonly commence therapy with either endothelin receptor antagonists or PDE5 [phosphodiesterase type 5] inhibitors." The consensus report also cautioned "against widespread treatment of non-PAH PH" until patient benefit has been proven in clinical trials. On the topic of combination therapy, the authors encouraged enrollment into RCTs evaluating combination therapy.

American College of Chest Physicians (ACCP)

In 2019, the American College of Chest Physicians (ACCP) updated their guidelines on pharmacologic therapy for PAH in adults. (22) Relevant new recommendations include:

- For patients with PAH who are treatment naive with WHO functional class (FC) II or class III symptoms, "an initial combination therapy with ambrisentan and tadalafil to improve 6MWD" is suggested (a weak recommendation with moderate quality evidence).
- "For stable or symptomatic PAH patients on background therapy with ambrisentan," a weak recommendation with low-quality evidence is made for the addition of tadalafil to improve 6MWD.
- To delay time to clinical worsening in PAH patients with WHO FC II symptoms, the guidelines recommend bosentan, macitentan, or riociguat (all ungraded consensus-based statements).
- To improve 6MWD for patients with WHO FC III symptoms, the guidelines recommend bosentan (strong recommendation, moderate quality evidence), ambrisentan (strong recommendation, low quality evidence), sildenafil (strong recommendation, low-quality evidence), or riociguat (ungraded consensus-based statement).
- To delay timely to clinical worsening in PAH patients with WHO FC III symptoms, the guidelines recommend macitentan, tadalafil, or riociguat (all ungraded consensus-based statements).
- For patients with PAH who are treatment-naive, have WHO functional class II or class III symptoms, and "who are not candidates for, or who have failed, CCB [calcium channel blocker] therapy," monotherapy with an "approved endothelin receptor antagonist (ETRA), phosphodiesterase-5 (PDE-5) inhibitor, or … riociguat" is advised for patients who are "unwilling or unable to tolerate combination therapy" with ambrisentan and tadalafil.
- For patients with PAH in WHO functional class III "who have evidence of rapid progression of their disease… "initial treatment with a parenteral prostanoid" should be considered." For patients with a "poor clinical prognosis despite treatment with one or two classes of oral agents," consideration of the "addition of a parenteral or inhaled prostanoid" is recommended.
- For patients with PAH who are treatment-naive and have WHO functional class IV symptoms, initial "therapy with a parental prostanoid agent" is recommended. If patients "are unable or do not desire to manage parenteral prostanoid therapy," combination treatment with "an inhaled prostanoid" and "an oral PDE5I and an E RA" is recommended.

In 2013, the ACCP and AHA released a joint policy statement, The Choosing Wisely Top Five List in Adult Pulmonary Medicine. (23) The list includes a recommendation to not routinely offer advanced vasoactive agents approved only for the management of PAH to patients with disease resulting from left heart disease or hypoxemic lung disease (group II or III PH).

American Thoracic Society

The American Thoracic Society (ATC), in their 2013 practice guideline on diagnosis, risk stratification, and management of PAH of sickle cell disease (SCD), strongly recommends against PAH-specific therapy "[f]or all patients with SCD with elevated TRV [tricuspid regurgitant velocity] alone or elevated NT-pro-BNP [N-terminal pro-brain natriuretic peptide] alone, and for patients with SCD with RHC [right heart catheterization]-confirmed PH with elevated pulmonary artery wedge pressure and low pulmonary vascular resistance." (24)

"However, for select patients with SCD with RHC-confirmed PH who have elevated pulmonary vascular resistance and normal pulmonary capillary wedge pressure, [the guidelines] make a weak recommendation for either prostacyclin agonist or endothelin receptor antagonist therapy and a strong recommendation against phosphodiesterase-5 inhibitor therapy."

In an official statement on PH phenotypes, the ATC (2014) asserts that "rapid advances in mechanistic understanding of PH, improved imaging methods and new modalities, and the emergence of innovative biomarkers…offer an opportunity to define PH phenotypes more precisely on the basis of pathobiology, which is crucial in such a heterogenous syndrome… Accurate phenotyping of PH can be used in research studies to increase homogeneity of study cohorts." (25)

"In addition, once the ability of the phenotypes to predict outcomes has been validated, phenotyping may also be useful for determining prognosis and guiding treatment." Defining phenotypes will enable testing "whether selective targeting of care" will afford the opportunity to use "the wide array of medications so that patients can live longer and more satisfying lives."

Ongoing and Unpublished Clinical Trials

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

Table 4. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04567602[a]	Non-Interventional Study on Pulmonary Arterial Hypertension Patients Treated With Macitentan Or Selexipag: Experience From an Italian Cohort (INSPECTIO)	200	Nov 2023
NCT05557942[a]	A Long-Term Extension, Multi-Center Safety Study of AV-101 in Subjects With Pulmonary Artierial Hypertension (PAH) Who Have Completed Study AV-101-002 (IMPAHCT-FUL)	462	Dec 2025

NCT05934526[a]	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oral Inhalation of Seralutinib for the Treatment of Pulmonary Arterial Hypertension (PAH)	350	Oct 2025
Unpublished			
NCT01908699[a]	A Multicenter, Double-blind, Randomized, Placebo-controlled, Phase 3 Study to Assess the Efficacy and Safety of Oral BPS-314d-MR added-on to Treprostinil, Inhaled (Tyvaso®) in Subjects With Pulmonary Arterial Hypertension	273	February 2019

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	E0779, E0780, J1325, J3285, K0455, S0155

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
12/31/2025	Document became inactive.
08/15/2024	Document updated with literature review. “Patient” changed to “individual” in coverage statement; intent unchanged. Added new references 1, 3, 5-6, and 21.
10/15/2023	Reviewed. No changes.
08/01/2022	Document updated with literature review. Coverage unchanged. No references added; one removed.

01/01/2022	Reviewed. No changes.
04/01/2020	Document updated with literature review. The following change was made to Coverage: Modified coverage statements to remove all mention of oral drugs, as coverage for oral drugs would be addressed under the applicable pharmacy benefit plan. References 8, 16, 20-23 added.
03/15/2018	Reviewed. No changes.
03/01/2017	Document updated with literature review. Coverage section revised to remove single agents approved by the FDA for treatment of PAH/WHO group 1. The following coverage statement: "The use of inhaled nitric oxide for treatment of PAH is considered experimental, investigational, and unproven." was removed from this medical policy and is now addressed on medical policy THE801.038.
02/01/2015	Document updated with literature review. The following changed in Coverage: 1) Criteria for oral drugs, including combination therapy, was removed from this policy (however, imatinib (oral) is considered experimental, investigational and/or unproven—this statement remains on this policy); 2) NOTE: Oral agents (e.g., bosentan, ambrisentan, macitentan, sildenafil, tadalafil, vardenafil, riociguat) are usually a pharmacy benefit, and should be referred to pharmacy. In addition, the title changed from Pulmonary Arterial Hypertension (PAH) Drug Therapies.
03/15/2012	Document updated with literature review, and substantially revised. The following was added to the Coverage section: 1) Flolan—language edited for long term treatment of PAH and PH associated with the scleroderma spectrum of disease; 2) Tyvasol—for treatment of PAH to increase walk distance; 3) Letairis—for treatment of PAH to improve exercise capacity and delay clinical worsening; 4) Combination therapy may be considered medically necessary for patients who fail to respond to a single medication, but is experimental, investigational and unproven as first line therapy; 5) The use of drug therapy that has not been FDA-approved is considered experimental, investigational and unproven, including but not limited to beraprost, vardenafil, and imatinib; 6) The list of experimental, investigational and unproven indications was edited to be consistent with new WHO Group language; 7) Tracleer may be considered medically necessary for treatment of PAH in patients with WHO Class II.
12/01/2009	Tadalafil added as a new, FDA-labeled, covered indication.
02/01/2008	Revised/updated entire document
11/15/2005	Revised/updated entire document
08/15/2003	New medical document