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Medication Policy Manual

Policy No: dru633

Topic: Medications for Pulmonary Arterial Hypertension (PAH)

Date of Origin: July 1, 2020

- Adempas, riociguat oral
- ambrisentan oral (generic, Letairis)
- bosentan oral (generic, Tracleer)
- Opsumit, macitentan oral
- Opsynvi, macitentan and tadalafil
- Orenitram, treprostinil oral
- Tyvaso / Tyvaso DPI, treprostinil inhalation
- Uptravi, selexipag oral
- Uptravi IV, selexipag injection
- Winrevair, sotatercept-csrk
- Yutrepia, treprostinil inhalation

Committee Approval Date: April 2, 2026

Next Review Date: 2027

Effective Date: June 1, 2026

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

This policy is for medications used in the treatment of pulmonary arterial hypertension (PAH) and other specific forms of pulmonary hypertension.

Policy/Criteria

Most contracts require pre-authorization approval of medications for pulmonary arterial hypertension (PAH) prior to coverage.

I. Continuation of therapy (COT): Medications for PAH may be considered medically necessary for COT when criterion A, B or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1, 2, and 3 below must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

AND

3. **For branded bosentan (Tracleer) or branded ambrisentan (Letairis) only**: There is clinical documentation (such as chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (bosentan or ambrisentan).

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve): Medications for PAH (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (such as chart notes) that criterion A, B, or C below are met.

A. **Pulmonary arterial hypertension** (PAH) - Medications for PAH (as listed in *Table 1*), when criteria 1 and 2 below are met:

1. There is a diagnosis of **WHO Group 1 pulmonary arterial hypertension** (PAH) (see *Appendix I*). Note: This criterion is NOT met for patients with a diagnosis of pulmonary hypertension (PH), but group unspecified, or with the diagnostic workup ongoing.

AND

2. For the following medications only, specific criteria for PAH must also be met:

Medication	Criteria
• Opsumit (macitentan) • Opsynvi (macitentan and tadalafil)	**a.** Bosentan and ambrisentan have been ineffective, not tolerated, or are contraindicated.
Letairis (branded ambrisentan)	**a.** Bosentan has been ineffective, not tolerated, or contraindicated. **AND** **b.** There is clinical documentation (such as chart notes) of an intolerance or contraindication to an inactive ingredient in generic ambrisentan.
Tracleer (branded bosentan)	**a.** Ambrisentan has been ineffective, not tolerated, or contraindicated. **AND** **b.** There is clinical documentation (such as chart notes) of an intolerance or contraindication to an inactive ingredient in generic bosentan.
• Adempas (riociguat) • Uptravi (selexipag oral) • Orenitram (treprostinil oral)	**a.** Sildenafil or tadalafil have been ineffective, not tolerated, or are contraindicated. **AND** **b.** Bosentan or ambrisentan have been ineffective, not tolerated, or contraindicated. **AND** **c.** **For Orenitram (treprostinil oral) only**: will be used as monotherapy.
Winrevair (sotatercept)	**a.** Will be used as add-on therapy: Documentation that the patient is currently being treated with a double or triple regimen of at least **two** medications (from different classes) for PAH (as listed in *Appendix IV*) **AND** those PAH medications will be continued with Winrevair (sotatercept). **AND** **b.** Persistent PAH: Documentation of WHO functional class (FC) II or III (see *Appendix III*).

OR

B. **For Adempas (riociguat) only**: Pulmonary hypertension (PH) associated with chronic thrombotic and/or embolic disease (CTEPH) [WHO Group 4, see *Appendix II*], that is inoperable or with residual PH after pulmonary thromboendarterectomy (PTE).

OR

C. **For Tyvaso, Tyvaso DPI, Yutrepia (inhaled treprostinil) only**: Pulmonary hypertension (PH) associated with interstitial lung disease (PH-ILD) [WHO Group 3, see *Appendix II*] when there is documentation or attestation of diffuse parenchymal disease, based on lung imaging.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers all oral, inhaled, and subcutaneous medications for PAH coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers all intravenous (IV) medications for PAH coverable only under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, medications for PAH will be authorized in quantities as listed in *Table 1*.

TABLE 1. Medications for Pulmonary Arterial Hypertension (PAH)

Product	Quantity Limit
Adempas (riociguat oral)	90 tablets per month
ambrisentan oral (Letairis, generic)	30 tablets per month
bosentan oral (Tracleer, generic)	60 tablets per month
Opsumit (macitentan oral)	30 tablets per month
Opsynvi (macitentan and tadalafil)	30 tablets per month
Orenitram (treprostinil oral)	Up to 42 mg per day
Tyvaso (treprostinil inhalation)	28 ampules (81.2 mL) per 28 days
Tyvaso DPI (treprostinil inhalation)	Up to 224 cartridges per 28 days
Uptravi (selexipag oral)	Up to 3,200 mcg per day
Uptravi IV (selexipag injection)	Up to 60 of the 1,800 mcg vials per month

<table>
<tr><td>Winrevair (sotatercept subcutaneous)</td><td><u>0.3mg/kg dose (initial dose):</u>
<table><tr><th>Weight</th><th>Quantity</th></tr><tr><td>158 kg or less</td><td>One 45 mg kit (one 45mg vial) per 21 days</td></tr><tr><td>Above 158kg</td><td>One 60mg kit (one 60mg vial) per 21 days</td></tr></table>
<u>0.7mg/kg dose (target dose):</u>
<table><tr><th>Weight</th><th>Quantity</th></tr><tr><td>67 kg or less</td><td>45mg kit (one 45mg vial) per 21 days</td></tr><tr><td>68-89 kg</td><td>60mg kit (one 60mg vial) per 21 days</td></tr><tr><td>90-132 kg</td><td>90mg kit (two 45 mg vials) per 21 days</td></tr><tr><td>133 kg and above</td><td>One 120mg kit (two 60mg vials) per 21 days</td></tr></table></td></tr>
<tr><td>Yutrepia (treprostinil inhalation)</td><td>Up to 140 capsules per 28 days</td></tr>
</table>

D. Authorization:

1. **For Winrevair (sotatercept) only**:

a. <u>Initial authorization</u> shall be limited to 6 months.

b. <u>Reauthorization</u> **shall** occur every 12 months thereafter with clinical documentation (such as chart notes) that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

2. With the exception of Winrevair (sotatercept), Medications for PAH **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Bosentan (Tracleer, generic) is considered not medically necessary when used for essential hypertension.

V. Uptravi IV (selexipag injection) is considered not medically necessary (for outpatient use).

VI. Medications for PAH are considered investigational when used for all other conditions, unless specified above in the coverage criteria, including but not limited to:

A. All other types of pulmonary hypertension (PH) [WHO Groups 2-5, see *Appendix II*], including PH associated with the following (unless specified above in the coverage criteria):

1. Left heart disease, including congestive heart failure (CHF) [WHO Group 2].

2. Lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) [WHO Group 3] except as noted in the coverage criteria.

3. Miscellaneous causes, such as sarcoidosis (WHO Group 5).

B. **Specific oral therapies [Opsumit (macitentan), Opsynvi (macitentan and tadalafil), Adempas (riociguat), Uptravi (selexipag oral), Orenitram (treprostinil oral) only]**: Digital ischemia and/or ulcers, including Raynaud's phenomenon, due to systemic sclerosis, scleroderma, or other causes.

C. **Ambrisentan (Letairis, generic), Opsumit (macitentan), Opsynvi (macitentan and tadalafil), bosentan (Tracleer, generic), and Adempas (riociguat) only**: Idiopathic pulmonary fibrosis (IPF), with or without pulmonary hypertension.

D. **Adempas (riociguat) only**: Use in combination with any phosphodiesterase inhibitor, including sildenafil (generic Revatio), tadalafil (generic Adcirca), dipyridamole, or theophylline.

E. **Bosentan (Tracleer, generic) only**: Behçet's disease.

F. **Orenitram (treprostinil oral) only**: Use in combination with other PAH-specific medications, including all medications listed in Table 1, as well as sildenafil, tadalafil, epoprostenol injection, and treprostinil injection.

G. **Winrevair (sotatercept subcutaneous) only**: Use as monotherapy, in WHO Functional class I, or in treatment naive patients with PAH.

Position Statement

Summary

- The intent of this policy is to cover medications for PAH for the indications and doses for which they have been shown to be safe and effective, as detailed in the coverage criteria:
    * WHO Group 1 pulmonary arterial hypertension (PAH), when treatment with lower cost generic therapies are ineffective or not a treatment option.
    * Adempas (riociguat) only: Group 4 pulmonary hypertension (PH) associated with chronic thrombotic and/or embolic disease (CTEPH), when pulmonary thromboendarterectomy (PTE) is ineffective or not a treatment option.
    * Tyvaso, Yutrepia (treprostinil inhalation) only: Group 3 pulmonary hypertension (PH) associated with interstitial lung disease (ILD), with diffuse parenchymal disease, based on lung imaging.
    * Winrevair (sotatercept) only: as add-on therapy for persistent PAH (functional class II/III), despite current double or triple background PAH regimens.
- *Pulmonary Arterial Hypertension (PAH)*
    * There is insufficient evidence to establish any one oral therapy for PAH is clearly superior to another. Generic sildenafil is the lowest-cost oral medication for PAH and a treatment option for most treatment-naïve PAH patients, along with generic tadalafil, both phosphodiesterase-5 inhibitors (PDE5is).
    * Among the endothelin receptor antagonists (ERAs), generic ambrisentan and generic bosentan are the lowest cost. There is no evidence that any one ERA is safer or more effective than another. However, among the medications for PAH with an available generic product, including ambrisentan and bosentan (see *Table 1*), the generic product is the lower cost option. Therefore, the branded products are covered only when the generic equivalent is not a treatment option.
    * Injectable prostanoids epoprostenol and treprostinil are available as lower-cost generic options. The branded prostanoids (prostacyclin analogues or PCAs) for PAH [Tyvaso, Yutrepia (treprostinil inhalation), and Orenitram (treprostinil oral)] have been studied individually in the treatment of PAH. To date, there is insufficient evidence that any one of these products is safer or more effective than the other.
    * The addition of Orenitram (treprostinil oral) to other PAH-specific medications, such as oral phosphodiesterase-5 inhibitors (PDE5is) or endothelin-receptor antagonists (ERAs), has not been shown not improve exercise tolerance over monotherapies for PAH. [1 2]
    * New therapies [Adempas (riociguat), Uptravi (selexipag oral) and Orenitram (treprostinil oral)] are coverable when low-cost generics are not an option, given the lack of superiority to lower cost oral step therapy options, as well as lower cost generic PCAs. Adempas (riociguat) and Uptravi (selexipag oral) have been studied when used for PAH inadequately managed with oral PDE-5is and ERAs.

- *Other Coverable Pulmonary Hypertension Uses*
    * For pulmonary hypertension due to CTEPH, surgical clot removal with pulmonary thromboendarterectomy (PTE) is the treatment of choice and standard of care therapy. PAH-specific medication therapies may be considered for patients unable to have surgery or with residual PH; however, the evidence for efficacy is limited. All CTEPH patients should receive along with lifelong anticoagulation. [3] Adempas (riociguat) has been FDA-approved for and may be a treatment option for inoperable or recurrent CTEPH. Other PAH medications are being studied for use in CTEPH; however, there is insufficient evidence at this time to support the use of any other PAH medications for this indication.
    * Pulmonary hypertension (PH) due to interstitial lung disease (PH-ILD) is a specific type of PH associated with fibrotic lung disease. Tyvaso and Yutrepia (treprostinil inhalation) have been FDA-approved for and may be a treatment option for PH-ILD. Other PAH medications are being studied for use in PH-ILD; however, there is insufficient evidence at this time to support the use of any other PAH medications for this indication.
- The World Health Organization (WHO) classifies pulmonary hypertension (PH) in five groups, based on underlying etiology of PH. [4]
    * Group 1 (pulmonary arterial hypertension) patients have generally irreversible, progressive disease and may require treatment with PAH-specific therapies.
    * For patients with Groups 2-5, PH may be reversible. Therapy should be directed at treating the underlying cause, such as clot removal for PH due to chronic thromboembolic (CTEPH) with pulmonary thromboendarterectomy (PTE). For pulmonary hypertension due to lung disease (Group 3 PH), the underlying lung disease should be treated, along with supportive therapies. [4 5]
- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin, and prostacyclin analogs (PCAs) [epoprostenol, treprostinil (generic Remodulin, Tyvaso, Yutrepia), Uptravi (selexipag)], endothelin-receptor antagonists (ERAs) [ambrisentan, bosentan, Opsumit (macitentan), Opsynvi (macitentan and tadalafil)], PDE-5 inhibitors (PDE5is) (sildenafil, tadalafil), the soluble guanylate cyclase stimulator (sGCs) Adempas (riociguat), and the activin signaling inhibitor Winrevair (sotatercept SC).
- For the treatment of PAH, a stepwise approach is generally used to manage patients. In early disease or with less severe symptoms, oral therapies are used. As symptoms progress, inhaled or injectable therapies, such as epoprostenol injectable and treprostinil injectable/inhaled may be used [4]
- Medications for PAH may be covered at the doses been shown to be effective (as detailed in the coverage criteria). There is no insufficient evidence that doses of medications for PAH exceeding those listed in the coverage criteria provide any additional clinical benefit when used in the treatment of coverable indications.
- There is currently insufficient evidence, except as noted in the efficacy section below, for ambrisentan, bosentan, Uptravi (selexipag oral), or Orenitram (treprostinil oral) in patients with Groups 2-5 PH. In addition, medications for PAH may be harmful in some situations and raise the overall cost of care.

- The pivotal PAH trial of Adempas (riociguat) allowed use in combination with bosentan or inhaled prostanoids (PCAs). However, use of Adempas (riociguat) with any phosphodiesterase-5 inhibitor (e.g., sildenafil, tadalafil, dipyridamole, theophylline) is contraindicated due to excessive hypotension in combination.

Clinical Efficacy

- Medications for PAH are used for the treatment of pulmonary arterial hypertension (PAH), Adempas (riociguat) for both PAH and CTEPH, and Tyvaso and Yutrepia (treprostinil inhalation) for both PAH and PH-ILD to improve exercise ability, symptoms and time to clinical worsening. [6]
- For the covered indications, medications for PAH were found to improve performance on the 6-minute walk test, as well as symptoms (functional class) relative to placebo. The six-minute walk test (6MWD) is a measure of exercise tolerance and measures the distance that is covered in a 6-minute timeframe. Improvements in this test have been correlated to improved survival in PAH patients. WHO functional class is a measure of activity level and correlated with disease severity and outcomes but can be prone to reporting bias. The 6MWD is the standard used by the FDA for the approval of new drugs in the treatment of PAH; however, the clinical relevance of less than a 10% improvement in 6MWD is not known.

<u>Endothelin receptor antagonists (ERAs)</u>

- *Ambrisentan (generic, Letairis):* In two reliable pivotal randomized, controlled studies in adults with PAH found ambrisentan improved exercise capacity at 12-weeks, based on the six-minute walk test compared to placebo. [7 8]
- *Bosentan (generic, Tracleer):* In four unreliable randomized, controlled studies adults with PAH found bosentan may improve ability to exercise at 16-24 weeks based on 6MWD compared to placebo.[9-12] All of the studies were significantly flawed, due to short trial duration, incomplete reporting of results, high dropout rates, and use of a non-clinical primary endpoint (pulmonary vascular resistance index).
- *Opsumit (macitentan):* In one low confidence randomized, controlled study, in adults with PAH, Opsumit (macitentan) reduced occurrence of the primary endpoint compared to placebo. [13] The primary composite endpoint was time to death, a significant morbidity event or worsening of PAH (symptoms or the need for additional treatment). Significant events were defined as atrial septostomy, lung transplantation, or initiation of injectable prostacyclin and prostacyclin analogs (PCAs).
    * The majority of the benefit was in reduction in percentage of patients with PAH clinical worsening (-12.8% placebo-subtracted), which includes measurement of 6MWD. Effect on the rate of death and need for PCA therapy was small (absolute difference -0.2% and -2%). The trial was not powered for reduction of mortality, the most meaningful outcome for PAH.
    * Significant flaws in the trial included assessment bias for morbidity events, moderately high attrition and inclusion of few patients from North America. [14]
    * There are no head-to-head studies of Opsumit (macitentan) with other PAH therapies. However, 64% of the patients in the pivotal trial continued on stable

doses of PAH medications (61% PDE5is; 6% oral or inhaled PCAs). Opsumit (macitentan) has not been studied in combination with injectable PCAs [e.g., epoprostenol or treprostinil subcutaneous].

Combination Products

- *Opsynvi (macitentan and tadalafil):* The approval of Opsynvi (macitentan and tadalafil) was based on efficacy and safety data from studies to support the approval of Opsumit (macitentan) and Adcirca (tadalafil) individually. In an additional phase 3 trial including 187 patients with PAH, either treatment naïve or on background ERA or PDE5i therapy, Opsynvi (macitentan and tadalafil) demonstrated a 28% reduction in pulmonary artery resistance (PVR) compared to each macitentan or tadalafil *monotherapy* alone.[15 16] However, no studies have compared Opsynvi (macitentan and tadalafil) to a combination of Opsumit (macitentan) + tadalafil or any other ERA+PDE5i combination treatment; therefore, any difference in efficacy or safety between the combination product, Opsynvi (macitentan and tadalafil), and a combination of its individual components as separate products, is unknown. Soluble guanylate cyclase stimulator (sGCs)
- *Adempas (riociguat)*: The efficacy and safety of riociguat was evaluated in two published randomized, double-blind, placebo-controlled trials in both CTEPH (n =261) and PAH patients (n = 443). The primary endpoint for both trials was improvement in exercise capacity, as measured by six minute walking distance (6MWD), a validated surrogate marker for PH treatment response. [17 18]
    * CTEPH: [17]
        - All enrolled patients were ineligible for or had PH refractory to surgical clot resection (pulmonary endarterectomy).
        - Adempas (riociguat) was superior to placebo for improvement in 6MWD at 16 weeks (+ 46 meters (m), placebo-adjusted; mean baseline 347 m). In addition, symptoms (functional class) improved more frequently (33% vs. 15% placebo).
        - There are no trials of Adempas (riociguat) for CTEPH in combination with any other PAH medications.
    * PAH: [18]
        - The pivotal trial enrolled both patients naïve to PAH-specific therapy as well as those stable on PAH-specific medications, including ERAs or prostanoids (n=443).
            - Patients on PDE-5is were excluded, given the risk of hypotension when used with Adempas (riociguat). The majority of randomized patients (50%) were previously treated with an ERA or PCA and continued on therapy (44% bosentan, 6% non-intravenous PCA).
            - Adempas (riociguat) 2.5 mg three times daily was superior to placebo for improvement in 6MWD at 12 weeks (+ 36 m, placebo-adjusted; mean baseline 363 m). In addition, symptoms improved more frequently (21% vs. 14% placebo) and time to clinical worsening delayed.

- Subsequently, an open-label switch trial evaluated transition of patients with uncontrolled PAH symptoms on PDE-5 inhibitor (PDE5i) therapy to riociguat, as compared to continuation of baseline PDE-5 inhibitor therapy (n=226) [REPLACE]. [19] Of note, 71% of randomized patients were on both PDE-5 inhibitor (PDE5i) and ERA therapy at baseline.
- There is insufficient evidence to establish that Adempas (riociguat) is superior to PDE-5i or ERA therapy for PAH. Most patients in clinical trials were previously treated with a PDE-5i and/or ERA therapy. [18 19] Therefore, Adempas (riociguat) for PAH is coverable only after step therapy with both PDE-5i and ERA therapy.

Prostacyclin, and prostacyclin analogs (PCAs) (treprostinil and selexipag)

- *Injectable PCA (, treprostinil injection):* Pivotal trials for PAH suggested improvement in exercise capacity based on the 6MWD compared to placebo. [20 21]
- *Tyvaso, Utrepia (treprostinil inhalation):* The efficacy and safety of Tyvaso (treprostinil inhalation) was evaluated in two randomized, double-blind, placebo-controlled trials in both PH-ILD (n =326) and PAH (n = 235). [22 23] The primary endpoint for both trials was improvement in exercise capacity, as measured by 6MWD, a validated surrogate marker for PH treatment response. Of note, the FDA approval for Yutrepia (treprostinil inhalation) was based on Tyvaso (treprostinil inhalation) trial data.
  - PAH: Tyvaso (treprostinil inhalation) improved PAH symptoms based on exercise tolerance measured using 6MWD and quality of life in patients who remained symptomatic on bosentan or sildenafil; however, no other secondary endpoints were statistically significantly improved, such as time to clinical worsening, dyspnea, functional status, and other PAH signs and symptoms. The study was significantly flawed including excessive differential dropout rate between treatment arms (5.7%) combined with low overall completion rate of 86%, and short trial duration (only 12 weeks).
  - PH-ILD: Tyvaso (treprostinil inhalation) improved exercise tolerance using 6MWD; however, there is a lack of long-term data as well as evidence for improvement on overall quality of life and mortality. In addition, several study flaws, including the heterogeneity of ILD types in the clinical trial make it difficult to identify patients who would benefit most.
- *Orenitram (treprostinil oral):*
  - In one low-confidence randomized, controlled study in adults with PAH: [24]
    - The trial enrolled only patients naïve to PAH-specific therapy, as initial trials found no benefit from use of Orenitram (treprostinil oral) as add-on therapy.
    - Orenitram (treprostinil oral) up to 12 mg twice daily modestly improved 6MWD compared to placebo. The mean dose at week 12 was 3.4±1.9 mg twice daily.
    - However, the trial was not powered for reduction of mortality, the most meaningful outcome for PAH. This limited duration trial with a modest change in a surrogate endpoint provides little information about long-term treatment benefit.

- The study was significantly flawed, including a significant loss of the intent-to-treat population, moderately high attrition, differential loss, and a protocol amendment post-randomization.

* There is insufficient evidence to establish that Orenitram (treprostinil oral) is superior to PDE-5i or ERA therapy for PAH. There are no head-to-head studies of Orenitram (treprostinil oral) with other PAH therapies. Therefore, Orenitram (treprostinil oral) for PAH is coverable only after step therapy with both PDE-5i and ERA therapy.

* Orenitram (treprostinil oral) has not been proven effective as add-on therapy to other PAH-specific medications. In two Phase 3 trials, addition of Orenitram (treprostinil oral) did not significantly increase 6MWD in patients on a PDE5i, ERA, or both as compared with placebo (10 to 11 meters more than placebo). [1 2] A third combination therapy study protocol was withdrawn, prior to trial enrollment. [25]

- *Uptravi (selexipag oral):*

* The efficacy of Uptravi (selexipag oral) was initially established as add-on therapy for PAH. In the pivotal randomized, controlled study of adults (n=1,156) with previously treated PAH, Uptravi (selexipag oral) up to 1,600 mcg twice resulted in a 40% reduction in the occurrence of the primary endpoint compared to placebo. [GRIPHON] [26]
  - The trial enrolled both patients naïve to PAH-specific therapy as well as those stable on PAH-specific medications. The majority of randomized patients (80%) continued on stable doses of PAH medications (15% ERAs, 32% PDE-5is; both 33%).
  - The primary composite endpoint was time to death, a significant morbidity event or disease progression (symptoms or the need for additional treatment). Significant events were defined as hospitalization, atrial septostomy, lung transplantation, or initiation of injectable prostacyclin/prostacyclin analogs (PCAs) or long-term oxygen. Disease progression was defined as a 15% decrease in 6MWD accompanied by a worsening in WHO functional class or the need for additional treatment of PAH.
  - The majority of the benefit was in reduction in percentage of patients with hospitalization (-4.9% placebo-subtracted) and PAH clinical worsening (-10.6% placebo-subtracted), which includes measurement of 6MWD.
  - Effect on the rate of death and need for PCA therapy was small (absolute difference -1.8% and -0.5%). The trial was not powered for reduction of mortality, the most meaningful outcome for PAH.
  - The study was significantly flawed including assessment bias for morbidity events, moderately high attrition (19%), high differential attrition between treatment arms (> 5%), and inclusion of few patients from North America.

* Subsequently, one small (n=34) open-label, observational (single-arm) switch trial evaluated transition of patients with stable PAH symptoms on Tyvaso

(treprostinil inhalation) to Uptravi (selexipag oral) [TRANSIT-1]. [27]

- All patients were on at least one baseline oral PAH therapy (PDE-5i ERA, and/or sGC). Notably, 56% of patients were on both PDE-5i and ERA therapy.
- The trial did not compare Uptravi (selexipag oral) with any other therapies to allow any conclusion regarding comparative safety or efficacy.

* There is insufficient evidence to establish that Uptravi (selexipag oral) is superior to any other medication for PAH. There is insufficient data from head-to-head studies of Uptravi (selexipag oral) with other PAH therapies to establish superiority over other treatment options, including PDE-5is, ERAs, or other PCAs, as add-on therapy or as initial therapy.
  - Most patients in the available clinical trials were previously treated with PDE-5i and/or ERA therapy. [26 27] Therefore, Uptravi (selexipag oral) for PAH is coverable only after step therapy with both PDE-5i and ERA therapy.
  - One comparative RCT of double- versus triple-therapy in treatment-naïve patients with PAH compared PDE-5i/ERA (tadalafil, macitentan) with or without Uptravi (selexipag oral) [TRITON].[28] Both regimens were effective, but neither superior. Therefore, superiority of Uptravi (selexipag oral) remains unproven. A subsequent phase 4 trial found no difference in daily activity levels with addition of Uptravi (selexipag oral) to stable PDE-5i/ERA therapy. [29]

- Uptravi (selexipag oral) has not been studied in combination with other PCAs. One trial compared switch therapy from Tyvaso (treprostinil inhalation) to Uptravi (selexipag oral), but not combination therapy (detailed above). [27] The TRITON combination therapy trial did not include combination therapy with other PCAs (detailed above). [28]

Uptravi IV (selexipag injection)

- Subsequently, Uptravi IV (selexipag injection) was approved for short-term use in patients with PAH who were established and stable on Uptravi (selexipag oral). The approval was based on results from a small switch trial (n=20). The primary outcome for the 3-day trial was safety.[30]
- Use of Uptravi IV (selexipag injection) is considered "not medically necessary" for use in the outpatient setting and is not coverable for outpatient use.
  * All patients enrolled in the Uptravi IV (selexipag injection) trial were hospitalized for the IV infusions.
  * The FDA label specifies for use "in patients who are temporarily unable to take oral therapy." It is not labeled for self-administration or long-term use.

Activin Signaling Inhibitors

Winrevair [sotatercept subcutaneous (SC)]

- The available evidence for efficacy and safety of Winrevair (sotatercept SC) is limited to one pivotal phase 3, randomized, placebo-controlled trial in patients with persistent PAH despite current PAH-specific therapy (n=323). [31]

    * All enrolled patients had a confirmed diagnosis of PAH and documented persistent PAH symptoms, with a WHO functional class of II or III, despite stable PAH-specific therapies.
    * Patients were on stable background double or triple standard of care PAH-specific therapies. Winrevair (sotatercept SC) or placebo were started as add-on therapy to the double/triple PAH-specific therapy regimens.
    * The primary endpoint was the change from baseline at week 24 in the 6MWD, a validated measure of functional capacity and symptomatic improvement in daily activities in PAH patients. The primary endpoint favored Winrevair (sotatercept SC) over placebo with a difference of 40.8 meters in 6MWD (95% CI 28 to 54, p<0.001).
- The safety and efficacy of Winrevair (sotatercept SC) in settings other than those studied in the pivotal trial are unknown, including the following:
    * In treatment-naïve patients.
    * As monotherapy.
    * In less severe PAH (WHO functional class I).
    * In other types of pulmonary hypertension (WHO Group 2-5).
- At this time, there is no evidence to compare the safety or efficacy of add-on therapies for persistent PAH (patients on ≥ 2 PAH-specific therapies), including add-on Winrevair (sotatercept SC) versus standard of care add-on prostacyclin/prostacyclin analogs (e.g. injectable epoprostenol or treprostinil), which have years of safety and efficacy experience. However, Winrevair (sotatercept) is significantly higher cost as compared to usual dosing of treprostinil injection or epoprostenol injection. Therefore, as aligned with the available clinical trial evidence, Winrevair (sotatercept) is coverable only as add-on therapy in patients with persistent PAH (FC II/III) despite current regimens of ≥ 2 PAH-specific therapies.
- A randomized, phase 3 trial evaluated the use of sotatercept or placebo as an add-on treatment for patients with PAH. Approximately 74% and 26% of patients had WHO functional class III or IV, respectively. Patients were on maximally tolerated double or triple therapy for PAH and were at high risk of death. [32]
    * The primary endpoint was a composite of death from any cause, lung transplantation, or hospitalization for > 24 hours due to worsening PAH.
    * At the planned interim analysis, at least one primary endpoint event occurred in 15 patients (17%) in the sotatercept group, and in 47 patients (54%) in the placebo group (hazard ratio 0.24, p<0.001).
    * Hospitalization for worsening PAH was the main driver of the primary composite endpoint result.
    * A secondary endpoint of overall survival did not show a statistically significant difference between the sotatercept and placebo treatment groups.
    * Several trial concerns affect the interpretation and quality of evidence: early trial termination precludes longer-term assessment of safety and efficacy (median duration of follow up was 8.9 months, with an imbalance in duration of follow up between treatment groups), efficacy analysis was done in all intent-to-treat

patients (regardless of whether any trial intervention was received), and limited generalizability to those with less severe disease (not at high risk of death).

Guidelines

- Pulmonary arterial hypertension guidelines from the 2019 CHEST Guideline and Expert Panel Report [33]
    * Guidelines recommend the use of medications for PAH in WHO Group 1 PAH (see Appendix I) based on systematic review of the literature.
    * Graded recommendations and ungraded consensus statements for specific therapy are rated based on the available evidence.
    * For treatment-naïve individuals with WHO functional class (FC) I, continued monitoring is recommended for the development of symptoms what would signal disease progression and warrant initiation of pharmacotherapy (ungraded consensus-based statement).
    * For treatment-naïve PAH patients with WHO functional class (FC) II/III:
        ○ For individuals who are willing or able to tolerate combination therapy, a recommendation for combination therapy with ambrisentan and tadalafil is listed (weak recommendation, moderate quality evidence). For individuals unwilling or unable to tolerate combination therapy, a recommendation for monotherapy with either bosentan, macitentan, ambrisentan, riociguat, sildenafil, or tadalafil is listed, with no specific preference for one monotherapy agent over another.
    * For PAH patients with WHO FC IV symptoms and select WHO FC III (with rapid disease progression or poor prognostic markers) initial therapy with an injectable prostacyclin analog is listed, based on consensus. Inhaled or injectable prostacyclin may be added for WHO FC III patients with progressive symptoms despite one or two classes of oral PAH medications.
    * For uncontrolled PAH FC III/IV, step-wise approach to add-on therapy is advised, with most suggested therapies based on consensus statement.
    * Guidelines have not been updated since the approval of Winrevair (sotatercept).
- For suspected PH due to interstitial lung disease (PH-ILD), a specific subset of PH due to lung disease (PH Group 3), guidelines recommend: [4]
    * Management approach includes optimal treatment of the fibrotic lung disease and supportive therapies when indicated (e.g., oxygen, diuretics).
    * Additionally, referral to pulmonary rehabilitation and evaluation for lung transplantation are recommended in appropriate cases.
    * Of note: Guidelines for PH Group 3 (2009) have not been updated since the approval of Tyvaso or Yutrepia (treprostinil inhalation) for PH-ILD.
- Management of CTEPH consensus statement (ISHLT): [34]
    * Medications for PAH, including sildenafil, bosentan, Adempas (riociguat), and treprostinil injection, have been studied in CTEPH patients who are not candidates for surgery [pulmonary thromboendarterectomy (PTE)] and those

with residual PH after PTE. However, Adempas (riociguat) remains the only FDA-approved agent for inoperable or residual/recurrent CTEPH following PTE.

* There is currently no evidence to support using targeted PH therapy before PTE in patients with operable CTEPH, meaning use prior to (or in lieu of) surgery.

Safety

- Endothelin receptor antagonists (ambrisentan, bosentan, and macitentan) and Adempas (riociguat) have boxed warnings in their labeling for an increased risk of embryo-fetal toxicity.
- Bosentan (generic, Tracleer), and Adempas (riociguat) are only available through a Risk Evaluation and Mitigation Strategy (REMs) program, to educate patients about the risks fetal toxicity and ensure they are not used in pregnant women, due to the risk of fetal harm. The bosentan (generic, Tracleer) REMs program also requires monitoring for liver dysfunction. [35]
- Coadministration of phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline), with Adempas (riociguat) is contraindicated, due to additive hypotension leading to a high rate of discontinuation. [6] In addition, there was one death possibly related to the combination of riociguat and sildenafil. Warnings and precautions for Winrevair (sotatercept SC) include increased hemoglobin levels, thrombocytopenia, bleeding risk (mainly epistaxis and gingival bleeding) and telangiectasia. [36]

Investigational Uses

- Guidelines do not support the use of PAH medications for treatment of pulmonary hypertension (PH) in WHO Groups 2-5 (unless noted above), including PH related to chronic left heart disease (WHO Group 2) or chronic hypoxic states (WHO Group 3). Instead, these patients require optimization of therapies targeting their underlying disease state. [4]
- Raynaud's phenomenon: [25]
    * Trials of Adempas (riociguat) in Raynaud's phenomenon, for improvement of digital blood flow, are ongoing. Adempas (riociguat) was not found to significantly improve modified Rodnan skin scores (mRSS) versus placebo in patients with systemic sclerosis (SSc).[37]
    * Uptravi (selexipag oral) had no benefit over placebo in reducing the frequency of Raynaud's phenomenon attacks related to systemic sclerosis (SSc) in one placebo-controlled trial.[38]
    * Orenitram (treprostinil oral) is being studied in patients with digital ulcers and/or digital ischemia related to Raynaud's phenomenon, systemic sclerosis (SSc), or scleroderma, to improve peripheral blood flow and reduce digital ulcers. Results are not yet available. [25 39 40]

- Idiopathic pulmonary fibrosis (IPF):
    * The use of ambrisentan (generic, Letairis) is contraindicated in patients with IPF. [6] A placebo-controlled trial in patients with idiopathic pulmonary fibrosis (IPF), with or without pulmonary hypertension (WHO Group 3), found ambrisentan increased the risk of disease progression or death versus placebo.
    * One placebo-controlled study of bosentan (generic, Tracleer) in patients with idiopathic pulmonary fibrosis (IPF) (n=158) found no significant difference between bosentan and placebo treatment based on improvement in exercise capacity (6-minute walk distance).[41] A subsequent larger trial failed to demonstrate delays in IPF worsening or death with bosentan.[42]
    * A phase 2b placebo-controlled study of Adempas (riociguat) in patients with IPF was terminated early due to an increased number of deaths and no benefit for 6MWD. [43]
    * A phase 2b placebo-controlled study evaluated sildenafil as add-on therapy to Esbriet (pirfenidone) in patients with IPF. There was no benefit with sildenafil for the composite primary endpoint (disease progression and all-cause mortality).[44]
- Valvular heart disease: Use of sildenafil in patients with persistent pulmonary hypertension after valvular heart disease surgery [PH related to chronic left heart disease (WHO Group 2)] was associated with worse outcomes as compared to placebo. [45]
- CTEPH: One small (n=28) phase 2 trial of Uptravi (selexipag oral) for CTEPH failed to meet the primary endpoint [change in pulmonary vascular resistance (PVR)]. [46] A subsequent larger (n=78) phase 2 trial met the primary endpoint of PVR, but not the secondary health outcomes of 6MWD and WHO functional class. [47]
- Behçet's disease: One small randomized, placebo-controlled trial (n=10) found no reduction in disease activity with bosentan (Tracleer, generic) in patients with Behçet's disease.[48]

Cross References
Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension, BlueCross BlueShield Association (BCBSA) Medical Policy, MPRM 5.01.09 [December 2026]

Appendix I: Revised World Health Organization (WHO) Classification of pulmonary hypertension (PH) – Group 1 [4]

Group 1. Pulmonary arterial hypertension (PAH)

- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH):*
    - Connective tissue disorder (e.g., rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, systemic sclerosis (formerly known as CREST syndrome)
    - Congenital systemic-to-pulmonary shunts (e.g., congenital heart disease (CHD), including atrial or ventricular septal defect, patent ductus arteriosus (PDA), patent foramen ovale (PFO), truncus arteriosus, Eisenmenger syndrome, tetralogy of Fallot, transposition of the great vessels)
    - Portal hypertension
    - HIV infection
    - Drugs and toxins (e.g., anorexic agents, cocaine, methamphetamine, L-tryptophan)
    - Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies (e.g., sickle cell anemia, thalassemia), chronic myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
    - Pulmonary veno-occlusive disease (PVOD)
    - Pulmonary capillary hemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn

* Diagnoses, include, but are not limited to these common diagnoses.

Appendix II: Revised WHO Classification of PH – Groups 2-5 [4]

Group 2. Pulmonary hypertension with left heart disease

- Left-sided atrial or ventricular heart disease (systolic dysfunction, diastolic dysfunction)
- Left-sided valvular heart disease

Group 3. Pulmonary hypertension associated with lung diseases and/or hypoxemia

- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease (e.g., idiopathic pulmonary fibrosis)
- Sleep disordered breathing (e.g., obstructive sleep apnea (OSA))
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Group 5. Miscellaneous

- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Appendix III: Functional Status with Heart Failure

World Health Organization (WHO) functional class (FC) assessment classification: [49]

Class I: Patients with pulmonary hypertension (PH) but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.

Class II: Patients with PH resulting slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class III: Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.

Class IV: Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by physical activity.

New York Heart Association (NYHA) Heart Failure Classification: [50]

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 with 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 discomfort and symptoms occur at rest.

Appendix IV: Components of double or triple therapy regimens to which Winrevair (sotatercept) is added

Pharmacologic Class	Drug name (active ingredient)
Phosphodiesterase inhibitors	Sildenafil Tadalafil
Endothelin receptor antagonists	Bosentan Ambrisentan Macitentan
Prostacyclin pathway agonists	Treprostinil Selexipag
Soluble guanylate cyclase stimulators	Riociguat

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Revision History

Revision Date	Revision Summary
4/2/2026	• Clarified step therapy for brand name Letairis and Tracleer (no change to intent). • WHO FC IV removed from investigational uses for Winrevair (sotatercept) given new, yet very limited, evidence in this population. • Clarified that double or triple regimens to which Winrevair (sotatercept) is added must include medications from different classes (no change in intent). • Tyvaso and Tyvaso DPI QL sections updated to include all available pack sizes (no change to intent).
7/22/2025	Added Yutrepia (treprostinil inhalation), a new formulation, to policy at parity with Tyvaso (treprostinil inhalation).
4/3/2025	• Ventavis removed from policy as it was discontinued 5/2024.
6/20/2024	• Added Opsynvi (macitentan and tadalafil), a newly approved combination product, to coverage criteria. • Added Winrevair (sotatercept), a newly approved subcutaneous agent, for use as an add-on to current dual or triple standard of care background PAH regimens, in those with WHO functional class II or III only. • Added Tyvaso DPI (treprostinil inhalation) to policy.
03/21/2024	• Updated coverage criteria/step therapy for Adempas (riociguat), Uptravi (selexipag oral), and Orenitram (treprostinil oral) to include tadalafil in criterion i and use of *either* generic ambrisentan OR generic bosentan in criterion ii.
3/16/2023	• Clarification of step therapy for branded medications with an available generic, to be consistent with COT criteria. • Added bosentan for Behçet's disease to "Investigational Uses."
3/18/2022	Effective 6/1/2022: • Clarification of Continuation of Therapy (COT) criteria, with addition of step therapy for branded medications with an available generic. • Added Uptravi IV, a newly approved formulation. Use of Uptravi IV is considered "not medically necessary" in the outpatient setting. Use in the acute (inpatient) setting is not subject to pre-authorization UM review.

Revision Date	Revision Summary
	• Add step therapy with bosentan and ambrisentan for coverage of highest cost options (Uptravi, Orenitram, and Adempas). • Removed treprostinil injection (generic, Remodulin) from the policy (no UM).
7/16/2021	Effective 10/1/2021: • Removed sildenafil step therapy requirement from criteria for oral endothelin receptor antagonists (ERAs). • Added step therapy with generic treprostinil injection as a requirement for coverage of brand treprostinil injection (Remodulin). • Added coverage criteria for use of Tyvaso (treprostinil inhalation) in pulmonary hypertension (PH) associated with interstitial lung disease (PH-ILD), a newly FDA-approved indication.
4/22/2020	New policy (effective 7/1/2020). Replaces individual drug coverage policies for medications for PAH (dru218, dru219, dru220, dru221, dru222, dru322, dru324, dru337, dru446). No change to intent of coverage from previous: limits coverage to patients with Group 1 PAH (or CTEPH for riociguat only), step therapy with low-cost generics for oral medications for PAH (sildenafil, ambrisentan and bosentan) and use of quantity limits.

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