Drug and Biologic Coverage Policy

Effective Date **1/1/2024**
Next Review Date **1/1/2025**
Coverage Policy Number **6121**

Pulmonary Hypertension (PH) Therapy

Table of Contents

Related Coverage Resources

Avanafil (IP0100)
Sildenafil (Viagra) [IP0098]
Tadalafil (Cialis) for Employer Group Plans [IP0097]
Tadalafil (Cialis) for Individual and Family Plans [IP0101]
Vardenafil (IP0099)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

This coverage policy addresses the use of oral phosphodiesterase-5 (PDE5) inhibitors (sildenafil, tadalafil) for pulmonary arterial hypertension. The use of oral PDE5 inhibitors for other uses is addressed in a separate coverage policy (including Adcirca or Revatio use in Raynaud's phenomenon). Please refer to the related coverage policy link above.

Oral PH Therapy	Inhaled PH Therapy	Parenteral PH Therapy
• **Adcirca®** (tadalafil) • **Adempas®** (riociguat) • **Alyq** (tadalafil) • **ambrisentan** • **bosentan** • **Letairis®** (ambrisentan) • **Opsumit®** (macitentan) • **Orenitram®** (treprostinil) • **Revatio®** (sildenafil) • **sildenafil** • **tadalafil**	• **Tyvaso®** (treprostinil) • **Tyvaso DPI™** (treprostinil) • **Ventavis®** (iloprost)	• **epoprostenol** • **Flolan®** (epoprostenol) • **Remodulin®** (treprostinil) • **Revatio®** (sildenafil) • **treprostinil** • **Veletri®** (epoprostenol) • **Uptravi®** (selexipag)

Oral PH Therapy	Inhaled PH Therapy	Parenteral PH Therapy
• **Tadliq®** (tadalafil) • **Tracleer®** (bosentan) • **Uptravi®** (selexipag)		

Other therapies used for pulmonary hypertension management are available that do not require medical necessity review (for example, calcium channel blockers).

Pulmonary Hypertension (PH) therapy is considered medically necessary in Adults and Pediatrics when ALL of the following criteria are met:

- Diagnosis of PH is documented by right heart catheterization or echocardiogram
- Prescriber of therapy should be (or prescribed in coordination with) a pulmonologist, cardiologist or rheumatologist
- Drug or biologic specific criteria are met as below:

Product	Criteria for Use
Adcirca (tadalafil)	**For Employer Group Plans:** Documentation of **ALL** of the following: 1. Treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) 2. Trial of tadalafil (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction 3. Will not be used in combination with a guanylate cyclase stimulator (for example: riociguat) **For Individual and Family Plans:** Documentation of **ALL** of the following: 1. Treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) 2. Trial of tadalafil (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction 3. Will not be used in combination with a guanylate cyclase stimulator (for example: riociguat)
ambrisentan	Treatment of PAH (WHO Group 1)
bosentan	Treatment of PAH (WHO Group 1)
epoprostenol	Documenation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Absence of congestive heart failure caused by reduced left ventricular ejection fraction
Flolan (epoprostenol)	Documenation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Absence of congestive heart failure caused by reduced left ventricular ejection fraction
Letairis (ambrisentan)	**For Employer Group Plans:** Documentation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Trial of ambrisentan (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction **For Individual and Family Plans:** Documentation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1)

Product	Criteria for Use
	2. Trial of ambrisentan (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction
Orenitram (treprostinil)	Treatment of PAH (WHO Group 1)
Remodulin (treprostinil)	**For Employer Group Plans and Individual and Family Plans:** Documentation of **BOTH** of the following (1 and 2): 1. Treatment of PAH (WHO Group 1) 2. **ONE** of the following (A, B, or C): A. The individual has tried **treprostinil** (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction B. The request is for Remodulin subcutaneous infusion AND the individual does not have and cannot obtain a compatible pump (CADD-MS-3) that allows generic treprostinil to be administered C. Individual is currently receiving Remodulin therapy
Revatio (sildenafil) **injection**	Documentation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) in an individual established on treatment with oral sildenafil or Revatio 2. Individual is temporarily unable to take oral medication 3. Individual has an intolerance to sildenafil injection 4. Will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)
Revatio (sildenafil) **oral suspension**	**For Employer Group Plans:** Documentation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. **BOTH** of the following: A. Individual has an inability to use sildenafil tablets (generic Revatio) B. Trial of sildenafil oral suspension (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction 3. Will not be used in combination with a guanylate cyclase stimulator (for example, riociguat) **For Individual and Family Plans:** Documenation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Individual has an inability to use sildenafil tablets (generic Revatio) 3. Will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)
Revatio oral tablets (sildenafil)	Documentation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Trial of sildenafil oral tablets (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction 3. Will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)
sildenafil injection	Documenation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) in an individual established on treatment with oral sildenafil or Revatio 2. Individual is temporarily unable to take oral medication 3. Will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)

Product	Criteria for Use
sildenafil oral suspension	Documenation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Individual has an inability to use sildenafil tablets (generic Revatio) 3. Will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)
sildenafil oral tablets	Documenation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)
tadalafil / Alyq	Documenation of **ALL** of the following: 1. Treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) 2. Will not be used in combination with a guanylate cyclase stimulator (for example: riociguat)
Tadliq (tadalafil)	**For Employer Group Plans:** Documentation of **ALL** of the following: 1. Treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) 2. Will not be used in combination with a guanylate cyclase stimulator (for example: riociguat) 3. **ONE** of the following: A. Individual has an inability to swallow tadalafil tablets (generic Adcirca) [may require prior authorization] B. Individual is unable to achieve the desired dose with tadalafil tablets (generic Adcirca) [may require prior authorization] **For Individual and Family Plans:** Documenation of **ALL** of the following: 1. Treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) 2. Will not be used in combination with a guanylate cyclase stimulator (for example: riociguat) 3. **ONE** of the following: A. Individual has an inability to swallow tadalafil tablets (generic Adcirca) [may require prior authorization] B. Individual is unable to achieve the desired dose with tadalafil tablets (generic Adcirca) [may require prior authorization]
Tracleer (bosentan)	**For Employer Group Plans:** Documenation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Trial of bosentan oral tablets (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction [applies to Tracleer 62.5 mg, 125 mg tablets only]. **For Individual and Family Plans:** Documentation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Trial of bosentan oral tablets (the bioequivalent generic product) AND cannot take due to a formulation difference in the inactive ingredient(s) which would result in a significant allergy or serious adverse reaction [applies to Tracleer 62.5 mg, 125 mg tablets only].
treprostinil injection	Treatment of PAH (WHO Group 1)

Product	Criteria for Use
Tyvaso (treprostinil) **Tyvaso DPI** (treprostinil)	Documentation of **ONE** of the following (1 or 2): 1. Treatment of PAH (WHO Group 1) 2. Treatment of Interstitial Lung Disease Associated Pulmonary Hypertension (PH-ILD) WHO Group 3* when **ALL** of the following are met (A, B, C, D, and E): A. Individual is 18 years of age or older B. Individual with connective tissue disease are required to have a baseline forced vital capacity < 70% C. Individual has evidence of diffuse parenchymal lung disease on computed tomography of the chest D. Individual meets **BOTH** of the following criteria (i and ii): i. A right heart catheterization has been performed ii. Results of the right heart catheterization confirm the diagnosis of WHO Group 3 interstitial lung disease associated with pulmonary hypertension E. Prescribed by, or in consultation with, a cardiologist, a pulmonologist or a rheumatologist *Note: This involves diagnosis such as idiopathic interstitial pneumonia, combined pulmonary fibrosis and emphysema, WHO Group 3 connective disease, and chronic hypersensitivity pneumonitis.
Veletri (epoprostenol)	Documentation of **ALL** of the following: 1. Treatment of PAH (WHO Group 1) 2. Absence of congestive heart failure caused by reduced left ventricular ejection fraction
Ventavis (iloprost)	Treatment of PAH (WHO Group 1)

Cigna covers the drugs or biologics listed below as medically necessary for the treatment of Pulmonary Hypertension (PH) in Adults when ALL of the following are met:

- Diagnosis of PH is documented by right heart catheterization or echocardiogram
- Prescriber of therapy should be (or prescribed in coordination with) a pulmonologist, cardiologist or rheumatologist
- Drug or biologic specific criteria are met as below:

Adempas (riociguat)	Documentation of **ONE** of the following: 1. Treatment of PAH (WHO Group 1) in an adult (18 years and older) **AND** will not be used in combination with a phosphodiesterase-5 inhibitor (e.g., sildenafil, tadalafil) 2. Treatment of persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) in an adult (18 years and older) either after surgical treatment or if inoperable CTEPH **AND** will not be used in combination with a phosphodiesterase-5 inhibitor (e.g., sildenafil, tadalafil)
Opsumit (macitentan)	Treatment of PAH (WHO Group 1)
Uptravi (selexipag) oral tablets	Treatment of PAH (WHO Group 1)
Uptravi (selexipag) intravenous infusion	Documentation of **BOTH** of the following (1 and 2): 1. Treatment of Pulmonary Arterial Hypertension, World Health Organization (WHO) Group 1 2. **ONE** of the following (A or B): A. Individual is currently receiving Uptravi tablets and is unable to continuing taking Uptravi tablets

	B. Individual is currently receiving Uptravi intravenous infusion

Initial authorization is up to 12 months except for Tyvaso for PH-ILD (WHO Group 3), the initial authorization is 4 months.

Reauthorization is up to 12 months unless otherwise stated.

Pulmonary Hypertension therapy is considered medically necessary for continued use when the initial criteria are met.

Tracleer is considered not medically necessary for the treatment of Congestive Heart Failure with Left Ventricular Dysfunction as it was shown to not be beneficial.

Pulmonary Hypertension (PH) Therapy is considered experimental, investigational, or unproven for ANY other use, including the following:

- For all Pulmonary Hypertension products, except Adempas (riociguat): Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

When coverage is available and medically necessary, the dosage, frequency, duration of therapy and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Pulmonary Hypertension Therapy.

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

FDA Approved Indication

Brand Name	Approved Indication
Adcirca (tadalafil, Alyq)	Adcirca is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).
Adempas (riociguat)	Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class. Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).
Flolan (epoprostenol)	Flolan is indicated for the treatment of PAH (WHO Group I) to improve exercise capacity. Trials establishing effectiveness included predominantly (97%) patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).
Letairis (ambrisentan)	Letairis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and delay clinical worsening. Letairis is also indicated for the treatment of PAH in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (64%) or PAH associated with connective tissue diseases (32%).

Brand Name	Approved Indication
Opsumit (macitentan)	Opsumit is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to reduce the risks of disease progression and hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).
Orenitram (treprostinil)	Orenitram is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to delay disease progression and to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%).
Remodulin (treprostinil)	• Pulmonary Arterial Hypertension Remodulin is indicated for the treatment of PAH (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%). It may be administered as a continuous subcutaneous infusion or continuous intravenous (IV) infusion; however, because of the risks associated with chronic indwelling central venous catheters, including serious blood stream infections (BSIs), reserve continuous intravenous infusion for patients who are intolerant of the subcutaneous route, or in whom these risks are considered warranted. • Pulmonary Arterial Hypertension in Patients Requiring Transition from Flolan® In patients with pulmonary arterial hypertension requiring transition from Flolan (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.
Revatio (sildenafil)	Revatio is indicated for the treatment of PAH (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%). Limitation of Use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.
Tadliq (tadalafil)	Tadliq is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).
Tracleer (bosentan)	Tracleer is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) • In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). • In pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

Brand Name	Approved Indication
	Considerations for use Patients with WHO Class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of hepatotoxicity in WHO Class II patients, which may preclude future use as their disease progresses.
Tyvaso (treprostinil) **Tyvaso DPI** (treprostinil)	**Pulmonary Arterial Hypertension** Tyvaso is indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability. Studies establishing effectiveness predominately included patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration. **Pulmonary Hypertension Associated with ILD** Tyvaso is indicated for the treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO Group 3) to improve exercise ability. The study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (IIP) (45%) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE) (25%), and WHO Group 3 connective tissue disease (22%).
Uptravi (selexipag)	Uptravi is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%).
Veletri (epoprostenol)	Veletri is indicated for the treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
Ventavis (iloprost)	Ventavis is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

Recommended Dosing

FDA Recommended Dosing

Brand Name	Recommended Dosing
Adcirca (tadalafil, Alyq)	The recommended dose of Adcirca is 40 mg (two 20 mg tablets) taken once daily with or without food. Dividing the dose (40 mg) over the course of the day is not recommended.
Adempas (riociguat)	The recommended starting dosage in adults is 1 mg taken 3 times a day. For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg taken three times a day. If systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension, up-titrate the dose by 0.5 mg taken three times a day. Dose increases should be no sooner than 2 weeks apart. The dose can be increased to the highest tolerated dosage, up to a maximum of 2.5 mg taken three times a

Brand Name	Recommended Dosing
	day. If at any time, the patient has symptoms of hypotension, decrease the dosage by 0.5 mg taken three times a day. For patients who are unable to swallow whole tablets, Adempas may be crushed and mixed with water or soft foods (such as applesauce) immediately before administration.
Flolan (epoprostenol)	Initiate intravenous infusions of Flolan at 2 ng/kg/min. Alter the infusion by 1-to 2ng/kg/min increments at intervals sufficient to allow assessment of clinical response. These intervals should be at least 15 minutes. During dose initiation, asymptomatic increases in pulmonary artery pressure coincident with increases in cardiac output may occur. In such cases, consider dose reduction, but such an increase does not imply that chronic treatment is contraindicated. Base changes in the chronic infusion rate on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse vasodilatory reactions. In general, expect progressive increases in dose. If dose-related adverse reactions occur, make dose decreases gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Avoid abrupt withdrawal of Flolan or sudden large reductions in infusion rates. Following establishment of a new chronic infusion rate, measure standing and supine blood pressure for several hours. Taper doses of Flolan after initiation of cardiopulmonary bypass in patients receiving lung transplants.
Letairis (ambrisentan)	Initiate treatment at 5 mg once daily, with or without tadalafil 20 mg once daily. At 4-week intervals, either the dose of Letairis or tadalafil can be increased, as needed and tolerated, to Letairis 10 mg or tadalafil 40 mg.
Opsumit (macitentan)	The recommended dosage of Opsumit is 10 mg once daily for oral administration. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended.
Orenitram (treprostinil)	Individualize dosing of Orenitram according to clinical response. The recommended starting dose of Orenitram is 0.25 mg twice daily (BID) with food, taken approximately 12 hours apart or 0.125 mg three times daily (TID) with food, taken approximately 8 hours apart. Increase the dose as tolerated to achieve optimal clinical response. The recommended increment is 0.25 or 0.5 mg BID or 0.125 mg TID every 3-4 days. If dose increments are not tolerated consider titrating slower. The maximum dose is determined by tolerability. The mean dose in a controlled clinical trial at 12 weeks was 3.4 mg BID. Maximum doses studied were 12 mg BID in the 12-week blinded study and up to 21 mg BID in an open-label long-term study. If intolerable pharmacologic effects occur, decrease the dose in increments of 0.25 mg. Avoid abrupt discontinuation. Transitioning from Subcutaneous or Intravenous Routes of Administration of Treprostinil • Decrease the dose of Remodulin while simultaneously increasing the dose of Orenitram. The dose of Remodulin can be reduced up to 30 ng/kg/min per day and the dose of Orenitram simultaneously increased up to 6 mg per day (2 mg TID) if tolerated. The following equation can be used to estimate a comparable total daily dose of Orenitram in mg using a patient's dose of IV/SC treprostinil (in ng/kg/min) and weight (in kg). • Orenitram total daily dose (mg) = 0.0072 x Remodulin dose (ng/kg/min) x weight (kg)

<table>
<tr><th>Brand Name</th><th>Recommended Dosing</th></tr>
<tr><td>Remodulin
(treprostinil)</td><td>Remodulin is indicated for subcutaneous (SC) or intravenous (IV) use only as a continuous infusion. Remodulin is preferably infused subcutaneously, but can be administered by a central intravenous line if the subcutaneous route is not tolerated, because of severe site pain or reaction. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated because of systemic effects, the infusion rate should be reduced to 0.625 ng/kg/min.

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while minimizing excessive pharmacologic effects of Remodulin (headache, nausea, emesis, restlessness, anxiety and infusion site pain or reaction).

The infusion rate should be increased in increments of 1.25 ng/kg/min per week for the first four weeks of treatment and then 2.5 ng/kg/min per week for the remaining duration of infusion, depending on clinical response. Dosage adjustments may be undertaken more often if tolerated. Avoid abrupt cessation of infusion. Restarting a Remodulin infusion within a few hours after an interruption can be done using the same dose rate. Interruptions for longer periods may require the dose of Remodulin to be re-titrated.</td></tr>
<tr><td>Revatio
(sildenafil)</td><td>Tablets and Oral Suspension: The recommended dose of Revatio is 5 mg or 20 mg three times a day (TID). Administer Revatio doses 4-6 hours apart. In the clinical trial no greater efficacy was achieved with the use of higher doses. Treatment with doses higher than 20 mg TID is not recommended.

Injection: Revatio injection is for the continued treatment of patients with PAH who are currently prescribed oral Revatio and who are temporarily unable to take oral medication. The recommended dose is 2.5 mg or 10 mg administered as an intravenous bolus injection three times a day (TID). The dose of Revatio injection does not need to be adjusted for body weight. A 10 mg dose of Revatio injection is predicted to provide pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.</td></tr>
<tr><td>Tadliq
(tadalafil)</td><td>The recommended dose of Tadliq is 40 mg (10 mL) taken once daily with or without food.</td></tr>
<tr><td>Tracleer
(bosentan)</td><td>Administer Tracleer orally following the dosing recommendations listed in the table below.

Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of hepatotoxicity.

<table>
<tr><th></th><th>Initial 4 weeks</th><th>Maintenance (after 4 weeks)</th></tr>
<tr><td>Patients >12 years of age and >40 kg</td><td>62.5 mg twice daily</td><td>125 mg twice daily</td></tr>
<tr><td>Patients >12 years of age and</td><td>62.5 mg twice daily</td><td>62.5 mg twice daily</td></tr>
<tr><td>Patients ≤12 years of age
≥4-8 kg
>8-16 kg
>16-24 kg
>24-40 kg</td><td>
16 mg twice daily
32 mg twice daily
48 mg twice daily
64 mg twice daily</td><td>
16 mg twice daily
32 mg twice daily
48 mg twice daily
64 mg twice daily</td></tr>
</table></td></tr>
<tr><td>Tyvaso
(treprostinil)</td><td>Usual Dosage in Adults
Tyvaso is intended for oral inhalation using the Tyvaso Inhalation System, which consists of an ultrasonic, pulsed delivery device and its accessories.
Tyvaso is dosed in 4 separate, equally spaced treatment sessions per day, during waking hours. Each treatment session will take 2 to 3 minutes. The treatment sessions should be approximately 4 hours apart.</td></tr>
</table>

<table>
<tr><th>Brand Name</th><th>Recommended Dosing</th></tr>
<tr><td></td><td>Initial Dosage:
Therapy should begin with 3 breaths of Tyvaso (18 mcg of treprostinil) per treatment session 4 times daily. If 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths, as tolerated.

Maintenance Dosage:
Dosage should be increased by an additional 3 breaths per treatment session, 4 times daily at approximately 1- to 2-week intervals. Studies establishing effectiveness in patients with PAH and PH-ILD have used target doses of 9 to 12 breaths per treatment session, 4 times daily. If adverse effects preclude titration to target dose, Tyvaso should be continued at the highest tolerated dose.

If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose.</td></tr>
<tr><td>Tyvaso DPI
(treprostinil)</td><td>Usual Dosage in Adults
Use Tyvaso DPI only with the Tyvaso DPI Inhaler. Tyvaso DPI is administered using a single inhalation per cartridge. Administer Tyvaso DPI in 4 separate, equally spaced treatment sessions per day, during waking hours. The treatment sessions should be approximately 4 hours apart.

Initial Dosage:
Tyvaso DPI therapy should begin with one 16 mcg cartridge per treatment session, 4 times daily.

Maintenance Dosage:
Increase dosage by an additional 16 mcg per treatment session at approximately 1- to 2-week intervals. The target maintenance dosage is usually 48 mcg to 64 mcg per session. If adverse effects preclude titration, continue Tyvaso DPI at the highest tolerated dose. If a scheduled treatment session is missed, resume therapy as soon as possible at the usual dose</td></tr>
<tr><td>Uptravi
(selexipag)</td><td><u>Uptravi Film-coated Tablets</u>
The recommended starting dose of Uptravi is 200 micrograms (mcg) given twice daily. Tolerability may be improved when taken with food. Increase the dose in increments of 200 mcg twice daily, usually at weekly intervals, to the highest tolerated dose up to 1,600 mcg twice daily. If a dose is reached that cannot be tolerated, the dose should be reduced to the previous tolerated dose. Do not split, crush, or chew tablets.

<u>Uptravi for Injection</u>
Use Uptravi for injection in patients who are temporarily unable to take oral therapy. Administer Uptravi for injection twice daily by intravenous infusion at a dose that corresponds to the patient’s current dose of Uptravi tablets (see Table 1). Administer Uptravi for injection as an 80-minute intravenous infusion.

Table 1: Dosing Table for intravenous based on current Uptravi tablets dose
<table>
<tr><th>Uptravi tablets dose (mcg) for twice daily dosing</th><th>Corresponding IV Uptravi Dose (mcg) for twice daily dosing</th><th>Reconstituted transfer volume (mL) for dilution</th></tr>
<tr><td>200</td><td>225</td><td>1.0</td></tr>
<tr><td>400</td><td>450</td><td>2.0</td></tr>
<tr><td>600</td><td>675</td><td>3.0</td></tr>
<tr><td>800</td><td>900</td><td>4.0</td></tr>
<tr><td>1000</td><td>1125</td><td>5.0</td></tr>
<tr><td>1200</td><td>1350</td><td>6.0</td></tr>
<tr><td>1400</td><td>1575</td><td>7.0</td></tr>
</table></td></tr>
</table>

Brand Name	Recommended Dosing
	1600 | 1800 | 8.0
Veletri (epoprostenol)	Initiate chronic infusion of Veletri at 2 ng/kg/min and increase in increments of 2 ng/kg/min every 15 minutes or longer until a tolerance limit to the drug is established or further increases in the infusion rate are not clinically warranted. If dose-limiting pharmacologic effects occur, then decrease the infusion rate until Veletri is tolerated. In clinical trials, the most common dose-limiting adverse events were nausea, vomiting, hypotension, sepsis, headache, abdominal pain, or respiratory disorder (most treatment-limiting adverse events were not serious). If the initial infusion rate of 2 ng/kg/min is not tolerated, use a lower dose. In the controlled 12-week trial in PAH/SSD, for example, the dose increased from a mean starting dose of 2.2 ng/kg/min. During the first 7 days of treatment, the dose was increased daily to a mean dose of 4.1 ng/kg/min on day 7 of treatment. At the end of week 12, the mean dose was 11.2 ng/kg/min. The mean incremental increase was 2 to 3 ng/kg/min every 3 weeks. *Dosage Adjustments*: Base changes in the chronic infusion rate on persistence, recurrence, or worsening of the patient's symptoms of pulmonary hypertension and the occurrence of adverse events due to excessive doses of Veletri. In general, expect increases in dose from the initial chronic dose. Consider increments in dose if symptoms of pulmonary hypertension persist or recur. Adjust the infusion by 1- to 2-ng/kg/min increments at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 minutes. In clinical trials, incremental increases in dose occurred at intervals of 24 to 48 hours or longer. Following establishment of new chronic infusion rate, observe the patient, and monitor standing and supine blood pressure and heart rate for several hours to ensure that the new dose is tolerated. During chronic infusion, the occurrence of dose-limiting pharmacological events may necessitate a decrease in infusion rate, but the adverse event may occasionally resolve without dosage adjustment. Make dosage decreases gradually in 2-ng/kg/min decrements every 15 minutes or longer until the dose-limiting effects resolve. Avoid abrupt withdrawal of Veletri or sudden large reductions in infusion rates. Except in life-threatening situations (e.g., unconsciousness, collapse, etc.), infusion rates of Veletri should be adjusted only under the direction of a physician. In patients receiving lung transplants, doses of epoprostenol were tapered after the initiation of cardiopulmonary bypass.
Ventavis (iloprost)	Ventavis is intended to be inhaled using the I-neb® AAD® System. The first inhaled dose should be 2.5 mcg (as delivered at the mouthpiece). If this dose is well tolerated, dosing should be increased to 5.0 mcg and maintained at that dose; otherwise maintain the dose at 2.5 mcg. Ventavis should be taken 6 to 9 times per day (no more than once every 2 hours) during waking hours, according to individual need and tolerability. The maximum daily dose evaluated in clinical studies was 45 mcg (5 mcg 9 times per day).

Drug Availability

Brand Name	Drug Availability
Adcirca (tadalafil, Alyq)	Adcirca (tadalafil) is supplied as 20 mg tablets (not scored), in bottles of 60 tablets. Generic tadalafil is available.
Adempas (riociguat)	Adempas is supplied as 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets. Females can only receive Adempas through the Adempas Risk Evaluation and Mitigation Strategy (REMS) Program, a restricted distribution program. Important requirements of the Adempas REMS Program include the following: • Prescribers must be certified with the program by enrolling and completing training.

Brand Name	Drug Availability
	• All females, regardless of reproductive potential, must enroll in the Adempas REMS Program prior to initiating Adempas. Male patients are not enrolled in the Adempas REMS Program. • Female patients of reproductive potential must comply with the pregnancy testing and contraception requirements. • Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Adempas.
Flolan (epoprostenol)	Flolan for injection is supplied as a sterile freeze-dried powder in 17-mL vials. Two 17-mL vials are available –one contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) and the other contains epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng). The Sterile Diluent for Flolan is supplied in vials containing 50-mL diluent. Generic epoprostenol sodium for injection is available.
Letairis (ambrisentan)	Letairis is available as 5 mg and 10 mg tablets. Generic ambrisentan tablets are available. For all females, Letairis is available only through a restricted program called the Letairis REMS, because of the risk of embryo-fetal toxicity. Notable requirements of the Letairis REMS program include the following: • Prescribers must be certified with the program by enrolling and completing training. • All females, regardless of reproductive potential, must enroll in the Letairis REMS program prior to initiating Letairis. Male patients are not enrolled in the REMS. • Females of reproductive potential must comply with the pregnancy testing and contraception requirements. • Pharmacies that dispense Letairis must be certified with the program and must dispense to female patients who are authorized to receive Letairis.
Opsumit (macitentan)	Opsumit is supplied as 10 mg tablets. For all females, Opsumit is available only through a restricted program called the Opsumit REMS Program, because of the risk of embryo-fetal toxicity. Notable requirements of the Opsumit REMS program include the following: • Prescribers must be certified with the program by enrolling and completing training. • All females, regardless of reproductive potential, must enroll in the Opsumit REMS Program prior to initiating Opsumit. Male patients are not enrolled in the REMS. • Females of reproductive potential must comply with the pregnancy testing and contraception requirements. • Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Opsumit.
Orenitram (treprostinil)	Orenitram is supplied as 0.125 mg, 0.25 mg, 1 mg, 2.5 mg, 5 mg tablets, and as titration kits for month 1, month 2 and month 3.
Remodulin (treprostinil)	Remodulin is supplied in 20 mL multidose vials containing 20, 50, 100, or 200 mg of treprostinil at concentrations of 1 mg/mL, 2.5 mg/mL, 5 mg/mL, and 10 mg/mL treprostinil, respectively, as sterile solutions in water for injection.
Revatio (sildenafil)	Revatio is supplied as 20 mg tablets in bottles of 90 tablets. Generic sildenafil (labeled for pulmonary arterial hypertension) is available as 20 mg tablets. Following reconstitution, Revatio powder for oral suspension is supplied as 112 mL (10 mg sildenafil/mL). Generic sildenafil oral suspension is available. Revatio injection is supplied as a single use vial containing 10 mg/12.5 mL of sildenafil.
Tadliq (tadalafil)	Tadliq is supplied as an Oral Suspension: 20 mg/5 mL.
Tracleer (bosentan)	Tracleer is available as 62.5 mg and 125 mg tablets, and as a 32.5 mg dispersible tablet for oral suspension. Generic bosentan is available for the 62.5 mg and 125 mg tablets.

Brand Name	Drug Availability
	Because of the risks of hepatotoxicity and birth defects, Tracleer is available only through a restricted program called the Tracleer REMS Program. The Tracleer REMS Program is a component of the Tracleer Risk Evaluation and Mitigation Strategy (REMS). Under the Tracleer REMS, prescribers, patients, and pharmacies must enroll in the program. Required components of the Tracleer REMS are: • Healthcare professionals who prescribe Tracleer must review the prescriber educational materials, enroll in the Tracleer REMS Program and comply with its requirements. • Healthcare professionals must (1) review serum aminotransferases (ALT/AST) and bilirubin, and agree to order and monitor these tests monthly; and (2) for females of childbearing potential, confirm that the patient is not pregnant, and agree to order and monitor pregnancy tests monthly. • To receive Tracleer, all patients must understand the risks and benefits and complete a patient enrollment form. • Pharmacies that dispense Tracleer must enroll in the program and agree to comply with the Tracleer REMS Program requirements.
Tyvaso (treprostinil)	Sterile solution for oral inhalation: 2.9 mL ampule containing 1.74 mg of treprostinil (0.6 mg per mL).
Tyvaso DPI (treprostinil)	Inhalation powder: Single-dose plastic cartridges containing 16, 32, 48, or 64 mcg of treprostinil as a dry powder formulation
Uptravi (selexipag)	Uptravi is available as 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg and 1,600 mcg tablets. Uptravi is available as 1800 mcg selexipag [Lyophilized powder white to almost white broken cake or powdered material, supplied in a 10 mL single-dose glass vial] for injection.
Veletri (epoprostenol)	Veletri is supplied as a sterile lyophilized material in 10 mL vials. Two 10-mL vials are available –one contains epoprostenol sodium equivalent to 0.5 mg (500,000 ng) and the other contains epoprostenol sodium equivalent to 1.5 mg (1,500,000 ng).
Ventavis (iloprost)	Ventavis is supplied in 1 mL ampules in two concentrations: 10 mcg/mL and 20 mcg/mL in cartons of 30 ampules.

General Background

Disease Overview

Pulmonary arterial hypertension is a heterogeneous group of progressive conditions, ultimately leading to right heart failure and death. (Galie, 2005) The primary physiologic characteristic of PAH is pulmonary vascular resistance (PVR). (Galie, 2005) The diagnosis of PAH must be confirmed with a complete right heart catheterization. (McLaughlin, 2009) The 2009 American College of Cardiology Foundation and American Heart Association (ACCF/AHA) Expert Consensus Document on Pulmonary Hypertension defines PAH as a mean pulmonary artery pressure (mPAP) greater than 25 mm Hg; a pulmonary capillary wedge pressure (PCWP), left atrial pressure, or left ventricular end-diastolic pressure (LVEDP) less than or equal to 15 mm Hg; and a pulmonary vascular resistance (PVR) greater than 3 Wood units. (McLaughlin, 2009) However, the 2007 American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines define PAH as a mPAP of at least 25 mmHg, with a PCWP of 15 mmHg or less. (Badesch, 2007)

Pulmonary hypertension is divided into 5 diagnostic groups based on similarities in pathophysiology, hemodynamic characteristics, and treatment options. (Simonneau, 2013) The diagnostics groups are commonly referred to as WHO (World Health Organization) groups.

WHO Group 1 (PAH)	**Pulmonary Arterial Hypertension (PAH)**: 1.1 Idiopathic 1.2 Heritable (BMPR2, ALK-1, ENG, SMAD9, CAV1, KCNK3) 1.3 Drug and Toxin-induced 1.4 Associated with: Connective Tissue disease (for example, scleroderma), HIV infection, Portal hypertension, Congenital heart

	diseases (for example, Eisenmenger), schistosomiasis 1' Pulmonary veno-occlusive disease (PVOD) and/or Pulmonary capillary hemangiomatosis (PCH) 1'' Persistent pulmonary hypertension of the newborn (PPHN)
WHO Group 2	**Pulmonary hypertension due to left heart disease:** 2.1 Left ventricular systolic dysfunction 2.2 Left ventricular diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
WHO Group 3	**Pulmonary hypertension due to lung diseases and/or hypoxia:** 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep-disordered breathing 3.5 Alveolar hypoventilation disorders 3.6 Chronic exposure to high altitude 3.7 Developmental lung diseases
WHO Group 4	**Chronic thromboembolic pulmonary hypertension (CTEPH)**
WHO Group 5	**Pulmonary hypertension with unclear multifactorial mechanisms:** 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental

BMPR2 – Bone morphogenic protein receptor type 2; ALK-1 – Activin-like receptor kinase-1; ENG – Endoglin; SMAD9 – Mothers against decapentaplegic; CAV1 – Caveolin-1; KCNK3 – Potassium channel super family K member-3.

Pulmonary hypertension due to interstitial lung disease (ILD) [WHO Group 3] can complicate the condition and is associated with an increased need for supplemental oxygen, reduced mobility, and decreased survival. (Waxman, 2021, King 2019, King 2020, Shioleno, 2021) Over 80% of patients with ILD can have pulmonary hypertension; (Waxman 2021) patients tend to be older and male. (Shioleno 2021) A recent definition is mPAP > 20 mmHg along with a pulmonary vascular resistance of ≥ 3 Wood units and a pulmonary artery occlusion pressure ≤ 15 mmHg at right-sided heart catheterization in the setting of chronic lung disease. (King 2019, King 2020, Shioleno, 2021) Severe restrictions on pulmonary function tests and marked fibrosis on computed tomography scans are distinctions. The exact etiology is unknown. The symptoms are non-specific and include increased dyspnea on exertion, cough, fatigue, chest pain, and lower extremity edema. Tyvaso is the only medication indicated for this specific use. Randomized controlled trials utilizing other pulmonary vasodilators indicated for patients with WHO Group 1 PAH in patients with ILD but have not shown clear benefit and some studies suggest harm with use of some medications (e.g., sildenafil, Tracleer® [bosentan tablets], ambrisentan, Adempas® [riociguat tablets], and Opsumit® [macitentan tablets]).

In addition to diagnostic grouping, PAH is also classified according to functional capacity using a modified New York Heart Association (NYHA) scale. (Montani, 2013) Functional capacity is ranked from I to IV, with class IV being the most severe. When classifying severity of PAH, this scale may be described as NYHA class or WHO functional class. Because the early signs and symptoms of PAH (e.g., dyspnea, fatigue, edema) are commonly associated with other diseases, early diagnosis of PAH is rarely achieved. (Hyduk, 2005) About 70% of patients with PAH have already progressed to functional class III or IV at the time of initial diagnosis. (Montani, 2013)

Modified New York Heart Association (NYHA) classification for pulmonary hypertension

CLASS I	Patients with pulmonary hypertension 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 pulmonary hypertension resulting in 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 pulmonary hypertension 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 pulmonary hypertension 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 any physical activity.

There is not a cure for PAH, but several treatment options for management are available. Goals of PAH therapy include delay in progression of disease, improvement of symptoms related to PAH, improvement in quality of life, and increased survival. (McLaughlin, 2009) Upon diagnosis and when not contraindicated, patients undergo a vasodilator test. Those patients who respond to this test may respond well to calcium-channel blocker (CCB) treatment. (McLaughlin, 2009; Taichman, 2014)

Pharmacology

- **Phosphodiesterase Type 5 Inhibitors (Adcirca, Revatio [sildenafil])**

Revatio and Adcirca are inhibitors of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by Revatio and Adcirca increase the concentration of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed.

- **Endothelin Receptor Antagonists (Letairis, Opsumit, and Tracleer)**

Endothelin-1 (ET-1) is a vasoconstrictor that binds to endothelin receptors (ETA and ETB) in human pulmonary arterial smooth muscle cells. This binding results in a restriction of blood flow through the pulmonary arteries. Antagonism of ETA and ETB in the pulmonary vasculature results in vasodilation and an increase in cardiac index. (Barst, 2009) Letairis (ambrisentan) is an ETA receptor antagonist with a high selectivity for the ETA versus ETB receptor. Tracleer (bosentan) is a specific and competitive antagonist at endothelin receptor types ETA and ETB with a slightly higher affinity for ETA receptors than for ETB receptors. Opsumit (macitentan) and an active metabolite act as antagonists on both ETA and ETB. Macitentan exhibits an extended occupancy period of the ET receptors in the pulmonary vasculature. (Actelion Pharmaceuticals US, Inc., 2013)

- **Prostanoids (Flolan [epoprostenol], Orenitram, Remodulin, Tyvaso, Veletri, and Ventavis)**

The prostanoids' major pharmacologic actions are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation. Oral treprostinil (Orenitram) is also noted to inhibit smooth muscle cell proliferation.

- **Prostacyclin Receptor Agonist (Uptravi)**

Selexipag is an oral selective prostacyclin IP receptor agonist. By stimulating the prostacyclin IP receptor, a vasodilatory and anti-thrombotic response is activated. While selexipag is active in its orally administered form, it undergoes hydrolysis to yield active metabolites which are 37 times more potent then selexipag at the IP receptor.

- **Soluble Guanylate Cyclase Stimulator (Adempas)**

Riociguat directly stimulates sCG. This stimulation ultimately leads to vasodilation. Additionally, riociguat stabilizes nitric oxide (NO) binding to sCG, thereby increasing the sensitization of sCG to endogenous NO. Riociguat administration has been shown to produce a direct relationship between plasma concentrations of the drug and certain hemodynamic parameters (e.g., systolic blood pressure, systemic vascular resistance, pulmonary vascular resistance, and cardiac output).

Professional Societies/Organizations

Adult

The 2009 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Expert Consensus Document and the 2014 American College of Chest Physicians (ACCP) guidelines provide treatment algorithms based on patient presentation. However, caution should be exercised when extrapolating treatment efficacy to other forms of PAH other than WHO diagnostic Group 1 because the majority of the literature for PAH treatment was conducted in patients with this classification of disease. (McLaughlin, 2009; Taichman, 2014) The decision to use PAH-specific therapy for WHO groups 2-5 should be made on a case-by-case basis by experienced pulmonary hypertension caregivers (McLaughlin, 2009).

- **American College of Cardiology Foundation and American Heart Association (ACCF/AHA) - 2009**

Bosentan, ambrisentan, sildenafil, and tadalafil are the oral PAH agents addressed in the ACCF/AHA Expert Consensus Document on Pulmonary Hypertension. Sitaxsentan is also included in these guidelines; however, it was removed from market in 2010. Macitentan, riociguat, and oral treprostinil are not included in these guidelines because they were not marketed in the United States at the time the guidelines were published. These guidelines also discuss the use of epoprostenol or treprostinil parenterally and inhaled iloprost. Treprostinil inhaled and selexipag are not included in these guidelines because these agents were not yet approved. CCBs are first-line therapy in patients with a positive vasoreactivity test. Patients with a negative vasoreactivity test are categorized based on prognosis – good (lower-risk) or poor (higher-risk) – as determined by clinical assessment. Risk level is determined by clinical evidence of right ventricular failure, progression of symptoms, WHO class, 6-minute walk distance, cardiopulmonary exercise test, echocardiography, hemodynamics, and brain natriuretic peptide concentrations. In lower-risk patients, an oral ERA (bosentan or ambrisentan) or oral PDE5I (sildenafil or tadalafil) is recommended as first-line therapy. Epoprostenol intravenous, treprostinil intravenous or subcutaneous (SC), or iloprost inhaled is recommended after failure of first-line therapy. In higher-risk patients, continuous treatment with an intravenous prostanoid (epoprostenol or treprostinil) is recommended as first-line treatment. In higher-risk patients, alternative options include iloprost inhaled, treprostinil SC, or an oral ERA or PDE5I. After reassessment in both prognostic groups, consider combination therapy if response to monotherapy is not adequate. Atrial septostomy and lung transplantation are last resort treatment options if there is disease progression with medications. (McLaughlin, 2009)

Summary of American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Recommendations for Treatment of Pulmonary Arterial Hypertension (McLaughlin, 2009)

Disease Characteristic	Treatment
Acute vasoactive test	
Positive	CCB, oral; if no sustained response then treat per lower-risk or higher-risk
Negative	Assess if poor or good prognosis. See treatment options below.
Lower-risk (good prognosis)[a]	
WHO class II or III	First-line therapy: ERA or PDE_5I, oral
	Alternative options:[b] Iloprost inhaled Treprostinil SC Epoprostenol or treprostinil intravenous
	Consider combination therapy if response to monotherapy is not adequate.
Higher-risk (poor prognosis) [a]	
WHO class IV	First-line therapy: epoprostenol or treprostinil intravenous
	Alternative options:[b] Iloprost inhaled Treprostinil SC

Disease Characteristic	Treatment
	ERA or PDE_5I oral
	Consider combination therapy if response to monotherapy is not adequate.
	Atrial septostomy or lung transplantation if disease progression with pharmacotherapy.

Abbreviations: CCB = calcium channel blocker, ERA = endothelin receptor antagonist, PDE_5I = phosphodiesterase-5 inhibitor, SC = subcutaneous
NOTE: These guidelines do not specifically address therapy for functional class I.
[a]Prognosis is based on clinical assessment.
[b]Choose alternative therapy if oral medications are not appropriate. Base therapy decision on patient profile and medication adverse effects.

- **American College of Chest Physicians (ACCP) – 2019**

In 2019, a CHEST guideline and Expert Panel Report was released regarding pharmacologic therapy for PAH in adults. There are many recommendations. For the treatment of naïve patients with PAH with WHO functional class II and III, it is suggested to use initial combination therapy with Letairis and Adcirca to improve 6MWD (6-minute walk distance) (weak recommendation, moderate quality evidence). For treatment-naïve patients with PAH with WHO functional class II symptoms who are not candidates for, or who have failed CCB therapy, initiation with Letairis and Adcirca is recommended. For patients who are unwilling or unable to tolerate combination therapy, monotherapy with a currently approved ERA, PDE5 inhibitor, or Adempas® (riociguat tablets). Revatio and Adcirca are noted to improve 6MWD. For treatment-naïve patients with PAH who are WHO functional class III who are not candidates for, or who have failed CCB therapy, it is recommended that therapy be initiated with the combination of Letairis and Adcirca. For patients who are unwilling or unable to tolerate combination therapy, monotherapy with a currently approved ERA, a PDE5 inhibitor or Adempas is recommended. For these patients, Revatio is recommended to improve 6MWD and to improve WHO functional class. Adcirca is recommended to improve 6WMD, to improve WHO functional class and to delay the time to clinical worsening. Regarding patients with PAH who remain symptomatic on stable and appropriate doses of an ERA or a PDE5 inhibitor, Tyvaso or Ventavis are recommended to either improve 6MWD, WHO functional class, or to delay the time to clinical worsening. For patients with WHO functional class IV symptoms, for treatment naïve patients with PAH who are unable or do not desire to manage parenteral prostanoid therapy, treatment with an inhaled prostanoid in combination with an oral PDE5 inhibitor and an ERA is recommended. Many recommendations are made for combination therapy which incorporated PDE5 inhibitors. (Klinger, 2019)

- **World Symposium on Pulmonary Hypertension (2nd) - 2013**

An updated treatment algorithm by the WSPH states that patients with Functional Class II should be treated initially with oral therapies (e.g., Adempas, Revatio (sildenafil tablets and suspension [generic]), Adcirca [tadalafil tablets {generic}], Opsumit, Tracleer, and Letairis [ambrisentan tablets]). Ventavis and Tyvaso are recommended for patients in Functional Class III and IV. In situations of inadequate response, combination therapy (including double or triple therapy) is recommended. Diagnosis is confirmed by a right heart catheterization (Galie, 2013)

Pediatric

- **American Heart Association (AHA) and American Thoracic Society (ATS) Pediatric Pulmonary Hypertension Guideline – 2015**

The American Heart Association (AHA) and American Thoracic Society (ATS) guidelines focus on the diagnosis, evaluation, and treatment of pediatric pulmonary hypertension. The authors note several challenges unique to this particular population in terms of clinical study design and a much more diverse set of conditions resulting in pulmonary hypertension compared to adults. The authors state that due to these differences it is challenging to apply the same classification system or treatment modalities in adults and children. The AHA/ATS consensus published a PAH disease severity classification system to distinguish lower risk from higher risk patients. Several determinants of risk were identified including WHO class, presence of syncope, echocardiographic findings, 6MWD, and others. Based on the severity of these markers patients can be classified as low risk or high risk and treatment differs accordingly. (Abman, 2015)

Patients in a lower risk category who do not respond to calcium channel blockers in an acute vasoreactivity test should initiate treatment with an oral or inhaled ERA or a PDE-5 inhibitor. Patients classified in the higher risk category should initiate treatment with epoprostenol, IV or SQ treprostinil, and consideration can be given to combination treatment containing an ERA or PDE-5 inhibitor. The guidelines state additional studies regarding

the safety and efficacy of combination therapy are needed however a goal-directed approach to therapy in which medications are sequentially added in order to achieve the goal is appropriate. Because of the complex nature of pulmonary hypertension in children, the guidelines recommend outpatient treatment provided at multidisciplinary specialized pediatric centers. (Abman, 2015)

Guidelines briefly discuss the treatment of pulmonary hypertension outside of PAH and provide the following condition specific recommendations regarding PAH-specific therapy…

- Congenital Diaphragmatic Hernia (CDH) – Evaluation for long-term PAH-specific therapy for PH in infants with CDH should follow recommendations for all children with PH, which includes cardiac catheritization. Guidelines do not provide any recommendation or support for any class of PAH therapy in the treatment of CHD-PH and state the management of PH in CDH remains controversial.

- Bronchopulmonary Dysplasia (BPD) – Evaluation and treatment of lung disease, including assessments for hypoxemia, aspiration, structural airway disease, and the need for changes in respiratory support, are recommended in infants with BPD and PH before initiation of PAH-targeted therapy. PAH-targeted therapy can be useful for infants with BPD and PH on optimal treatment of underlying respiratory and cardiac disease. Therapies discussed in the management of infants with BPD include iNO, sildenafil, ERAs, and CCBs. However, no recommendation is given regarding the use of a specific PAH therapy class.

- Acute Postoperative PH – In addition to conventional postoperative care, iNO or inhaled PGI_2 should be used as the initial therapy for PHCs (pulmonary hypertensive crisis) and right-sided heart failure. Sildenafil should be prescribed to prevent rebound PH in patients who have evidence of a sustained increase in PAP on withdrawal of iNO and require reinstitution of iNO despite gradual weaning of iNO dose.

- **Pediatric PDE5-inhibitor Safety and Efficacy**
  In August 2012, the FDA added a warning to the prescribing information stating that the use of Revatio (sildenafil) is not recommended in pediatric patients based on two clinical trials. In March 2014, the FDA clarified the recommendation noting that the purpose was to increase awareness of the clinical trial and not to indicate that Revatio should never be used in children and that there may be “situations in which the benefit-risk profile of Revatio may be acceptable in individual children”. (US FDA, 2014) In November 2015, the American Heart Association and American Thoracic Society published guidelines related to pediatric pulmonary hypertension diagnosis, evaluation, and treatment. In the guidelines, sildenafil is a recommended therapy in specific patient populations, based on data from clinical studies, including the two referenced above. (Abman, 2015)

  Unegbu and colleagues conducted a systematic review of the efficacy and safety of PDE-5 inhibitors in the pediatric pulmonary hypertension population. The review considered literature in which comparators were either no medication or other classes of medications used in the management of PH, leading to the inclusion of 21 studies (8 randomized, 13 observational, 9 retrospective, 4 prospective). The authors reported evidence that PDE-5 inhibitors, compared to either baseline or placebo, improve various parameters including echocardiography and oxygenation. Data also demonstrated safety of low to moderate doses of sildenafil in this age group. Due to a lack of extended pediatric pharmacokinetic studies of the oral PDE-5 inhibitors, the group offered no optimal dosing regimens. PDE-5 inhibitors are recommended as a component in the treatment of pediatric PH, owing of their efficacy in cardiovascular and oxygenation end points. Per the authors, additional controlled studies are necessary to outline the optimal treatment approach in this population. (Unegbu, 2017)

Medication	AHA/ATS Pediatric Guideline Recommended Dosing
PDE5 Inhibitors	
Adcirca (tadalafil)	Initial dose: 0.5 to 1 mg/kg/dose orally once daily

<table>
<tr><td></td><td>Maximum dose: 40 mg/day

Evaluated only in children >3 years of age</td></tr>
<tr><td>Revatio
(sildenafil)</td><td>Age <1 year: 0.5 to 1 mg/kg per dose orally three times per day

Age ≥1 year:
• <20 kg: 10 mg orally three times per day
• ≥20 kg: 20 mg orally three times per day

Avoid higher dosing in children because a greater risk of mortality was noted in the STARTS-2 study in children with PAH treated with high-dose sildenafil monotherapy
• High dose defined in trial as:

<table><tr><th>Body Weight (kg)</th><th>High Dose</th></tr><tr><td>≤ 20 kg</td><td>≥ 20mg three times per day</td></tr><tr><td>21 to 45 kg</td><td>≥ 40mg three times per day</td></tr><tr><td>> 45 kg</td><td>≥ 80mg three times per day</td></tr></table>
Delay use in extremely preterm infants until retinal vascularization is established</td></tr>
<tr><td colspan="2">ERAs (Endothelin Receptor Antagonists)</td></tr>
<tr><td>Letairis
(ambrisentan)</td><td>Maintenance dose:
▪ <20 kg: 2.5 to 5 mg orally once daily
▪ >20 kg: 5 to 10 mg orally once daily

Maximum dose: 10 mg/day

Avoid use in neonates and infants because glucuronidation is not mature</td></tr>
<tr><td>Tracleer
(bosentan)</td><td>*Since publication of guideline, Tracleer has received FDA indication for use in pediatrics 3 years and older, please refer to FDA Indication and Dosing sections of coverage polic</td></tr>
<tr><td colspan="2">Prostacyclin/Prostanoids</td></tr>
<tr><td>Flolan, Veletri
(epoprostenol)</td><td>Initial infusion rate: 1 to 2 ng/kg/min

Maintenance infusion rate: 50 to 80 ng/kg/min, titrated to effect

No clear maximum dose</td></tr>
<tr><td>Treprostinil</td><td>Remodulin (IV/SC)
• Starting dose: Up to 2 ng/kg/min
• Maintenance infusion rate: 50 to 80 ng/kg/min, titrated to effect
• No clear maximum dose

Tyvaso (inhaled)
• 1–9 patient-activated breaths every 6 hours

Orenitram (oral)
• Oral dosing not fully evaluated in children</td></tr>
<tr><td>Ventavis
(iloprost)</td><td>Initial dose: 2.5 mcg per inhalation 6 times a day

Uptitrate to 5 mg per inhalation 6 to 9 times per day as tolerated</td></tr>
</table>

- **European Paediatric Pulmonary Cardiovascular Disease Network - (2016)**

The expert consensus statement published by the European Paediatric Pulmonary Cardiovascular Disease Network reaffirms the AHA/ATS recommendations and also states that combination therapy with oral PAH agents in treatment-naïve pediatrics who are FC II or III may be considered. The consensus statement is

endorsed by the International Society of Heart and Lung Transplantation and the German Society of Pediatric Cardiology. (Hansmann, 2016)

Clinical Efficacy

Epoprostenol, Flolan, Veletri Contraindicated in CHF-LVD
As per the FDA product label for Flolan and Veletri, the chronic use of Flolan and Veletri in patients with heart failure due to severe left ventricular systolic dysfunction is contraindicated. A large trial evaluating the effect of Flolan on survival in NYHA Class III and IV patients with congestive heart failure due to severe left ventricular systolic dysfunction was terminated after an interim analysis of 471 patients revealed a higher mortality in patients receiving Flolan plus conventional therapy than in those receiving conventional therapy alone. Of note, the trial defined severe left ventricular systolic dysfunction as: : <25% within 3 months of enrollment, unless the patient was being treated with an intravenous inotropic agent, in which case a left ventricular ejection fraction of <30% was accepted. (FDA, 2012, 2015; Robert C., 1997)

Orenitram
Oral treprostinil is not addressed in clinical practice guidelines from the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) or the American College of Chest Physicians (ACCP). Three randomized, double-blind, placebo-controlled published trials evaluated the efficacy and safety of treprostinil diolamine compared to placebo. Two trials examined combination therapy of treprostinil diolamine on background therapy with ERAs or PDE5Is and one trial examined treprostinil diolamine monotherapy. The primary endpoint of all three trials was change in six minute walk distance (6MWD). Of these three trials, the treprostinil diolamine monotherapy trial showed a statistically significant change in 6MWD from baseline to week 12 with a median Hodges-Lehmann treatment effect of 23 meters (Jing, 2013). The other two studies did not achieve statistical significance of this outcome (Tapson, 2012; Tapson, 2013). No differences in clinical worsening were observed between treprostinil diolamine and placebo. Studies directly comparing treprostinil diolamine with other PAH treatments and studies evaluating the long-term efficacy and safety of treprostinil diolamine are ongoing.

Uptravi
Selexipag is not addressed in clinical practice guidelines from the American College of Cardiology Foundation and American Heart Association (ACCF/AHA) or the American College of Chest Physicians (ACCP). Clinical efficacy of selexipag was demonstrated in a multi-center, double-blind, placebo-controlled study enrolling 1,156 patients with a mean duration of treatment greater than 70 weeks. The study enrolled treatment naïve patients as well as those on stable background therapy of endothelin receptor antagonists or phosphodiesterase-5 inhibitors or a combination of the two. The primary end point of the study was the time to first occurrence of clinical worsening. Treatment with selexipag resulted in a 40% reduction of the occurrence of the primary endpoint compared to placebo. This benefit was consistent irrespective of patient's background therapy, etiology, and baseline functional class. A secondary endpoint of the study was 6MWD. Patients treated with selexipag achieved a four meter increase in 6MWD compared to a nine meter decrease in patients who received placebo. (McLaughlin, 2015)

Comparative Efficacy
- Few active-controlled trials have been conducted with oral or inhaled treatments for PAH although placebo-controlled trials are available for each drug. The SERAPH trial compared sildenafil with bosentan. Six-minute walk distance improved more with sildenafil 150 mg/day (+114 m, or +39%) than bosentan 250 mg/day (+59 m, or +19%, p = 0.044 vs. sildenafil) after 4 months of therapy. Quality of life also improved more with sildenafil (p = 0.002 vs. bosentan). However, changes in cardiac index, right ventricular mass, and systolic left ventricular eccentricity were similar in both groups. (Wilkins, 2005)
- Few clinical studies comparing efficacy between orally administered products have been conducted and as a result meta-analysis have been completed to help provide evidence in this area. Recently two meta-analysis have been conducted in this area with somewhat different results. One meta-analysis was conducted and included 18 randomized, double-blind, placebo-controlled trials in adults (n = 4,363) of oral PAH therapies (oral prostanoids, endothelin receptor antagonists [ERA], phosphodiesterase type 5 [PDE5] inhibitors, prostacyclin receptor agonists, and soluble guanylate cyclase stimulators). Primary outcome measure was

all-cause mortality. While none of the individual studies found a statistically significant reduction in mortality, evaluation by drug class demonstrated a reduction in mortality for PDE5 inhibitors compared to placebo. There was no statistical difference between treatment with ERAs or oral prostanoids and placebo. (Zheng, 2014) A second meta-analysis included 21 randomized, double-blind, placebo-controlled trials (n = 5,105) with a mean follow-up time of approximately five months. The primary endpoints were combined clinical worsening events and all-cause mortality. While reductions in the combined clinical worsening events were demonstrated for each class of medications, reductions in mortality were not significant for any class. (Zhang, 2015) The somewhat conflicting conclusion between meta-analyses and persistent lack of primary literature in this area further supports the need for additional research.

- A meta-analysis was conducted evaluating clinical worsening, WHO functional class improvement, and safety with sildenafil, iloprost, or bosentan. Eleven trials met the predefined inclusion criteria. There was no difference in the percentage of patients experiencing clinical worsening between bosentan (4%), sildenafil (5%), and iloprost (5%, p=NS). The percentage of patients with improvement in WHO functional class did not differ between bosentan (28%), sildenafil (35%), and iloprost (27%, p=NS). There were more reports of serious adverse events with iloprost (19%) compared with bosentan (6%) and sildenafil (1%, p<0.0001). The authors only compared each active agent with placebo for improvement in exercise tolerance. (He, 2010)
- A meta-analysis of 10 trials studied cardiopulmonary hemodynamics and predicted survival for bosentan, sitaxsentan, sildenafil, epoprostenol, beraprost, and treprostinil. No trials containing ambrisentan met inclusion criteria for this meta-analysis. Data for sitaxsentan will not be discussed because the agent was removed from the US market in 2010. Data for beraprost will not be discussed as this agent is not approved for use in the US. Cardiac index improved the most with bosentan (+0.5 L/min/m2), epoprostenol (+0.4 L/min/m2), and high-dose sildenafil (80 mg; +0.4 L/min/m2). Minor improvements in hemodynamic parameters occurred with low-dose sildenafil (20 mg; +0.2 L/min/m2). (Steele, 2010) The authors did not report a statistical analysis to support these statements. Predicted 3-year survival was calculated using the NIH Registry equation. This equation was based on mPAP, cardiac index, and mean right arterial pressure. (Thenappan, 2010) Predicted survival for each medication is listed as follows: bosentan (59%), epoprostenol (60%), treprostinil, route unspecified (57%), sildenafil 20 mg (55%), sildenafil 40 mg (60%), and sildenafil 80 mg (58%). (Steele, 2010)

- **Combination Therapy**

  Optimal combination regimens of the available treatment options for PAH remain undefined and there is limited data available supporting the use. The American College of Cardiology Foundation and American Heart Association (ACCF/AHA) recommends consideration of combination therapy for lower -risk (good prognosis, WHO class II or III) or higher-risk (poor prognosis, WHO class IV) if the response to monotherapy is inadequate. (McLaughlin, 2009) The American College of Chest Physicians (ACCP) provides recommendations for combination therapy based on current therapy, WHO functional class, and clinical status. (Klinger, 2019)

  The use of Adempas (riociguat) is contraindicated in combination with phosphodiesterase inhibitors (e.g., sildenafil [Revatio], tadalafil) due to hypotension. Of note, the FDA added a limitation of use to the indications section of the prescribing information for Revatio that adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity. (FDA, 2018)

  In October of 2015 the FDA approved the use of ambrisentan in combination with tadalafil to reduce the risk of disease progression and hospitalization for worsening pulmonary arterial hypertension, and to improve exercise ability. Safety and efficacy for this indication was demonstrated through a randomized, double-blind, active-controlled trial enrolling 605 patients with WHO Functional Class II or III. Patients were randomized to combination therapy with ambrisentan plus tadalafil or each medication given as monotherapy. The primary endpoint was time to first occurrence of clinical failure. Combination therapy was associated with a reduction in clinical failure compared to either product as monotherapy. (Galiè, 2015)

  Also in 2015 researchers were interested in combination therapy of bosentan plus sildenafil. A randomized, double-blind, active-controlled trial enrolling 334 patients in WHO functional class II to IV was conducted comparing combination bosentan plus sildenafil therapy to sildenafil monotherapy. The primary endpoint was defined as time to first morbidity or mortality event. A statistically significant difference in delaying the time to

first morbidity or mortality event was not demonstrated in the bosentan plus sildenafil treatment group compared to the sildenafil monotherapy group. Due to the conflicting results of combination therapy, additional research is needed in this area. (McLaughlin, 2015)

Not Medically Necessary Uses

- **Tracleer for treatment of CHF-LVD**

As per the FDA product label, Tracleer is not effective in the treatment of congestive heart failure with left ventricular dysfunction. In a pair of studies, 1613 subjects with NYHA Class III-IV heart failure, left ventricular ejection fraction <35%, on diuretics, ACE inhibitor, and other therapies, were randomized to placebo or Tracleer (62.5 mg twice daily titrated as tolerated to 125 mg twice daily) and followed for up to 70 weeks. Use of Tracleer was associated with no benefit on patient global assessment (the primary end point) or mortality. However, hospitalizations for heart failure were more common during the first 4 to 8 weeks after Tracleer was initiated. In a placebo-controlled trial of patients with severe chronic heart failure, there was an increased incidence of hospitalization for CHF associated with weight gain and increased leg edema during the first 4-8 weeks of treatment with Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure. (FDA, 2017; Packer, 2017))

Coding/ Billing Information

Note: Adcirca (tadalafil), Adempas (riociguat), Letairis (ambrisentan), Opsumit (macitentan), Orenitram (treprostinil diolamine), Revatio (sildenafil), Tracleer (bosentan), Tyvaso (treprostinil), Uptravi (selexipag), and Ventavis (iloprost) are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding and diagnosis codes, however, are generally not required for pharmacy claims submissions. All other products in this policy require medical drug coding and are listed as follows: Flolan (epoprostenol), Remodulin (treprostinil), Veletri (epoprostenol).

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
A7005	Administration set, with small volume nonfiltered pneumatic nebulizer, nondisposable
A7013	Filter, disposable, used with aerosol compressor or ultrasonic generator
A7014	Filter, nondisposable, used with aerosol compressor or ultrasonic generator
A7016	Dome and mouthpiece, used with small volume ultrasonic nebulizer
E0574	Ultrasonic/electronic aerosol generator with small volume nebulizer
J1325	Injection, epoprostenol, 0.5 mg
J3285	Injection, treprostinil, 1 mg
K0730	Controlled dose inhalation drug delivery system
S0155	Sterile dilutant for epoprostenol, 50 ml

References

1. Actelion Pharmaceuticals US, Inc. Opsumit (macitentan) tablets, for oral use [product information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; April 2019.
2. Actelion Pharmaceuticals US, Inc. Tracleer (bosentan) tablets, for oral use [product information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; May 2019.

3. Actelion Pharmaceuticals US, Inc. Uptravi (selexipag) tablets, for oral use and powder for intravenous infusion [product information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; July 2021.
4. Actelion Pharmaceuticals US, Inc. Veletri (epoprostenol) for injection [product information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; December 2018.
5. Actelion Pharmaceuticals US, Inc. Ventavis (iloprost) inhalation solution [product information]. South San Francisco, CA: Actelion Pharmaceuticals US, Inc.; October 2017.
6. Abman SH, Hansmann G, Archer SL, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015 Nov 24;132(21):2037-99
7. Badesch DB, Abman SH, Simonneau G, Rubin LJ, McLaughlin VV. Medical therapy for pulmonary arterial hypertension: updated ACCP evidence-based clinical practice guidelines. Chest 2007; 131 (6):1917-28.
8. Barst RJ, Gibbs JS, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. J Am Coll Cardiol. Jun 30 2009; 54(1 Suppl):S78-84.
9. Barst RJ, Ivy DD, Gaitan G, Szatmari A, Rudzinski A, Garcia AE, Sastry BK, Pulido T, Layton GR, Serdarevic-Pehar M, Wessel DL. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. Circulation. 2012; 125:324–334. doi:10.1161/CIRCULATIONAHA.110.016667.
10. Barst RJ, Beghetti M, Pulido T, Layton G, Konourina I, Zhang M, Ivy DD. STARTS-2: long-term survival with oral sildenafil monotherapy in treatment naive pediatric pulmonary arterial hypertension. Circulation 2014; 129:1914–1923.
11. Bayer HealthCare Pharmaceuticals Inc. Adempas (riociguat) tablets, for oral use [product information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; January 2018.
12. Eli Lilly and Company. Adcirca (tadalafil) tablets for oral administration [product information]. Indianapolis, IN: Eli Lilly and Company; May 2017
13. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol. Aug 2 2005; 46 (3):529-535.
14. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension (AMBITION). N Engl J Med. 2015(a);373(9):834-44
15. Galie N, Corris PA, Frost A, et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol. 2013; 62(25 Suppl):D60-D72.
16. Gilead Sciences, Inc. Letairis (ambrisentan) tablets, for oral use [product information]. Foster City, CA: Gilead Sciences, Inc.; March 2019.
17. GlaxoSmithKline. Flolan (epoprostenol sodium) for injection [product information]. Research Triangle Park, NC: GlaxoSmithKline; December 2018.
18. He B, Zhang F, Li X, et al. Meta-analysis of randomized controlled trials on treatment of pulmonary arterial hypertension. Circ J 2010; 74 (7):1458-1464.
19. Hoeper MM, Barbera JA, Channick RN, Hassoun PM, Lang IM, Manes A, Martinez FJ, Naeije R, Olschewski H, Pepke-Zaba J, Redfield MM, Robbins IM, Souza R, Torbicki A, McGoon M. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol. 2009; 54(1 Suppl):S85–96.
20. Hyduk A, Croft JB, Ayala C, Zheng K, Zheng ZJ, Mensah GA. Pulmonary hypertension surveillance--United States, 1980-2002. MMWR Surveill Summ. Nov 11 2005; 5 4(5):1-28.
21. Jing ZC, Parikh K, Pulido T, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. Circulation 2013; 127 (5):624-633.
22. King CS, Nathan SD. Pulmonary hypertension due to interstitial lung disease. Curr Opin Pulm Med. 2019; 25:459-467.
23. King CS, Shlobin OA. The trouble with Group 3 pulmonary hypertension in interstitial lung disease. Dilemmas in diagnosis and the conundrum of treatment. CHEST. 2020; 158(4):1651-1664.
24. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults. Update of the CHEST guideline and Expert Panel Report. CHEST. 2019; 155(3):565-586.
25. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. Circulation 2009; 119:2250-94.
26. McLaughlin V, Channick RN, Ghofrani HA, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. Eur Respir J. 2015; 46:405-413.

27. McLaughlin VV, Channick R, Chin K, et al. Effect of selexipag on morbidity/mortality in pulmonary arterial hypertension: Results of the GRIPHON study. J Am Coll Cardiol. 2015; 65(10_S): doi: 10.1016/S0735-1097(15)61538-8.
28. Montani D, Gunther S, Dorfmuller P, et al. Pulmonary arterial hypertension. Orphanet J Rare Dis 2013; 8 (1):97.
29. Packer M., McMurray J., Krum H., et al. Long-Term Effect of Endothelin Receptor Antagonism With Bosentan on the Morbidity and Mortality of Patients With Severe Chronic Heart Failure: Primary Results of the ENABLE Trials. JACC Heart Fail. 2017 May; 5(5):317-326.
30. Pfizer Inc. Revatio (sildenafil) tablets, for oral use/for oral suspension/injection, for intravenous use [product information]. New York, NY: Pfizer Inc. January 2019.
31. Robert C., Kirkwood A., William M., et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). AM Heart J. 1997 Jul; 134(1):44-54.
32. Rosenkranz S, Gibbs J, Wachter R, et al. Left ventricular heart failure and pulmonary hypertension. European Heart Journal, Volume 37, Issue 12, 21 March 2016, Pages 942-954.
33. Shioleno AM, Ruopp NF. Group 3 pulmonary hypertension: a review of diagnostics and clinical trials. Clin Chest Med. 2021; 42:59-70.
34. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013; 62: D34-41.
35. Steele P, Strange G, and Wlodarczyk J, et al. Hemodynamics in pulmonary arterial hypertension (PAH): do they explain long-term clinical outcomes with PAH-specific therapy? BMC Cardiovasc Disord 2010; 10:9.
36. Tapson VF, Jing ZC, Xu KF, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest 2013; 144 (3):952-958.
37. Tapson VF, Torres F, Kermeen F, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest 2012; 142 (6):1383-1390.
38. Taichman DB, Ornelas J, Chung L, et al. Pharmacologic therapy for pulmonary arterial hypertension in adults: CHEST Guideline and Expert Panel Report. Chest. 2014; 146 (2): 449-75.
39. Thenappan T, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Survival in pulmonary arterial hypertension: a reappraisal of the NIH risk stratification equation. Eur Respir J 2010; 35(5):1079-1087.
40. Unegbu C, Noje C, Coulson J, et al. Pulmonary Hypertension Therapy and a Systematic Review of Efficacy and Safety of PDE-5 inhibitors. Pediatrics. 2017 Mar; 139(3).
41. United Therapeutics Corp. Orenitram (treprostinil) extended release tablets for oral administration [product information]. Research Triangle Park, NC: United Therapeutics Corp; June 2017.
42. United Therapeutics Corp. Remodulin (treprostinil) injection [product information]. Research Triangle Park, NC: United Therapeutics Corp; July 2018.
43. United Therapeutics Corp. Tyvaso (treprostinil) inhalation solution, for oral inhalation only [product information]. Research Triangle Park, NC: United Therapeutics Corp; October 2017.
44. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA clarifies warning about pediatric use of Revatio (sildenafil) for pulmonary arterial hypertension. Silver Spring, MD: U.S. Food and Drug Administration: March 31, 2014. http://www.fda.gov/drugs/drugsafety/ucm390876.htm Accessed on June 3, 2014.
45. Waxman A, Restrepp-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. N Engl J Med. 2021; 384:325-334.
46. Wilkins MR, Paul GA, Strange JW, et al. Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension (SERAPH) study. Am J Respir Crit Care Med 2005; 171 (11):1292-1297.
47. Zhang HD, Zhang R, Jiang X, et al. Effects of oral treatments on clinical outcomes in pulmonary arterial hypertension: a systematic review and meta-analysis. Am Heart J. 2015; 170:96-103.e14.
48. Zheng YG, Ma H, Hu EC, et al. Oral targeted therapies in the treatment of pulmonary arterial hypertension: a meta-analysis of clinical trials. Pulm Pharmacol Therap. 2014; 29: 241-49.
49. Tyvaso DPI™ oral inhalation powder [prescribing information]. Danbury, CT and Research Triangle Park, NC: MannKind and United Therapeutics; May 2022.
50. Tadliq® oral suspension [prescribing information]. Farmville, NC: CMP; June 2022.