Drug and Biologic Coverage Policy

Effective Date 11/15/2025
Coverage Policy Number.....6121

Pulmonary Hypertension (PH) Therapy

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Related Coverage Resources

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Coverage Policy

Parenteral PH Therapy
• **Revatio®** (sildenafil) • **Sildenafil injection** • **Uptravi®** (selexipag)

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

Documentation: Documentation is required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, claims records, and/or other information.

Pulmonary Hypertension (PH) therapy is considered medically necessary in when ALL of the following criteria are met (1, 2 and 3):

1. Patient meets BOTH of the following (a and b):
    a. Patient has had a right heart catheterization **[documentation required]** (see documentation section above); AND
    b. The results of the right heart catheterization confirm the diagnosis of WHO Group 1 PAH; AND
2. The medication is prescribed by or in consultation with a cardiologist or a pulmonologist; AND
3. Drug or biologic specific criteria are met as listed in the below table(s)

Product	Criteria for Use
Revatio (sildenafil) **injection**	Patient meets **ALL** of the following (1, 2, 3 and 4): 1. Treatment of PAH (WHO Group 1) in an individual established on treatment with oral sildenafil or Revatio 2. Patient is temporarily unable to take oral medication 3. Patient has an intolerance to sildenafil injection 4. Revatio will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)
Sildenafil injection	Patient meets **ALL** of the following (1, 2, and 3): 1. Treatment of PAH (WHO Group 1) in an individual established on treatment with oral sildenafil or Revatio 2. Patient is temporarily unable to take oral medication 3. Sildenafil injection will not be used in combination with a guanylate cyclase stimulator (for example, riociguat)
Uptravi (selexipag) intravenous infusion	Patient meets **BOTH** of the following (1 and 2): 1. Treatment of Pulmonary Arterial Hypertension, World Health Organization (WHO) Group 1 2. Patient meets **ONE** of the following (A or B): A. Patient is currently receiving Uptravi tablets and is unable to continuing taking Uptravi tablets B. Patient is currently receiving Uptravi intravenous infusion

Initial authorization is up to 12 months.

Reauthorization is up to 12 months.

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

Conditions Not Covered

Pulmonary Hypertension (PH) Therapy for any other use is considered not medically necessary. Criteria will be updated as new published data are available.

FDA Approved Indications

FDA Approved Indication

Brand Name	Approved Indication
Revatio (sildenafil)	Adults Revatio is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group I) in adults to improve exercise ability and delay clinical worsening. Pediatric Patients (1 to17 years old)

Brand Name	Approved Indication
	Revatio is indicated in pediatric patients 1 to 17 years old for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underlie improvements in exercise.
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%).

Recommended Dosing

FDA Recommended Dosing

Brand Name	Recommended Dosing
Revatio (sildenafil)	**Recommended Dosage in Adults** Oral Dosage The recommended dosage of Revatio is 20 mg three times a day. Dose may be titrated to a maximum of 80 mg three times a day, if required, based on symptoms and tolerability. Although dose-response improvement in exercise ability was not observed in short-term studies in adults with PAH, the delay in clinical worsening with long-term use of sildenafil in Study A1481324 supports dosing up to a maximum of 80 mg three times a day. Intravenous Dosage The recommended dose is 10 mg administered as an intravenous bolus injection three times a day. 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. 2.2 **Recommended Dosage in Pediatric Patients** Oral Dosage The recommended dosage in patients ≤20 kg is 10 mg three times a day. For pediatric patients 20 kg to 45 kg, the recommended dosage is 20 mg three times a day. For pediatric patients 45 kg and greater, the recommended dosage is 20 mg three times a day. A maximum dose in pediatric patients has not been identified. Based on the experience in adults, dose may be titrated to a maximum of 40 mg three times a day for pediatric patients >45 kg, if required, based on symptoms and tolerability.
Uptravi (selexipag)	Uptravi Film-coated Tablets 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. Uptravi for Injection Use Uptravi for injection in patients who are temporarily unable to take oral therapy.

<table>
<tr><th>Brand Name</th><th>Recommended Dosing</th></tr>
<tr><td></td><td>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>
<tr><td>1600</td><td>1800</td><td>8.0</td></tr>
</table></td></tr>
</table>

Drug Availability

Brand Name	Drug Availability
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 with 90 mL of water, the total volume of the oral suspension is 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.
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.

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	**Pulmonary Arterial Hypertension (PAH)**:

(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.

- **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.

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 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)

<table>
<tr><th>Medication</th><th>AHA/ATS Pediatric Guideline Recommended Dosing</th></tr>
<tr><td colspan="2">PDE5 Inhibitors</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>
</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

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)

Coding/ Billing Information

Note: Letairis (ambrisentan), Opsumit (macitentan), Revatio (sildenafil), Tracleer (bosentan), and Uptravi (selexipag), 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.

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

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Revision Details

Type of Revision	Summary of Changes	Date
Selected revision	**Removed** Flolan, Remodulin, treprostinil injection, Tyvaso, Tyvaso DPI, Veletri, and Ventavis from the policy. **Added** a documentation statement. **Updated** the right heart catheterization statement. **Added** documentation to the right heart catheterization statement. **Updated** the specialist prescribing requirement.	11/15/2025

	Updated the Conditions Not Covered statement.	

The policy effective date is in force until updated or retired.