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Subject: Pulmonary Hypertension Drug Therapy

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement	Dosage/ Administration	Billing/Coding	Reimbursement	Program Exceptions	Definitions
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DESCRIPTION:

Pulmonary hypertension (PH) is a hemodynamic state defined by a resting mean pulmonary artery pressure at or above 25 mmHg. Because this definition is based on hemodynamic criteria, PH can be the result of a variety of disease of different causes. The [World Health Organization \(WHO\)](#) divides PH into five groups (Table 4) organized based on the cause of the condition and treatment options; it should be noted that while together all groups are called pulmonary hypertension, group 1 is called pulmonary arterial hypertension (PAH) and groups 2 through 5 are called pulmonary hypertension. The WHO functional classification (WHO-FC) of PH ([Table 5](#)) is a modification of the [New York Heart Association](#) functional class (Table 6).

Pharmacologic treatment of PAH is aimed primarily at vasodilation and includes calcium channel blockers, prostacyclin analogues (epoprostenol, iloprost, treprostinil), endothelin receptor antagonists (ambrisentan, bosentan), and phosphodiesterase-5 (PDE-5) inhibitors (sildenafil, tadalafil). Children with idiopathic PAH typically respond well to calcium channel blockers and are treated similarly to adults.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of pulmonary hypertension drug therapy **meets the definition of medical necessity** when **ALL** of the product specific criteria outlined in Table 1 are met.

Continuation of pulmonary hypertension drug therapy **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue in the past two years, **OR** the member has previously met all product specific initiation criteria
2. Treatment is prescribed or supervised by a cardiologist or pulmonologist with the following exception:
 - a. Indication for use is treatment of digital ulcers in members with systemic sclerosis
3. Member meets all product specific criteria outlined in Table 2

Table 1

Initiation criteria for use of pulmonary hypertension drug therapy	
Product Brand	Criteria
Ambrisentan <i>Letairis®</i>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC II or III symptoms (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist <ol style="list-style-type: none"> a. Member is not concomitantly taking another endothelin receptor antagonist (e.g. bosentan) 5. Dosage does not exceed 10 mg daily <p>Approval duration: 1 year</p>
Bosentan <i>Tracleer® tablets,</i> <i>Tracleer® tablets</i> <i>for oral suspension</i>	<p>Use meets the definition of medical necessity for either of the following indications if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) <ol style="list-style-type: none"> a. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> i. Right-heart cardiac catheterization

	<ul style="list-style-type: none"> ii. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age b. Member exhibits WHO-FC II, III or IV symptoms (Table 5) c. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) d. Prescribed by a cardiologist or pulmonologist <ul style="list-style-type: none"> i. Member is not concomitantly taking another endothelin receptor antagonist (e.g. ambrisentan) e. Dosage does not exceed 125 mg twice daily <p>2. Treatment of digital ulcers in members with systemic sclerosis</p> <p>Approval duration: 1 year</p>
<p>Sildenafil citrate</p> <p><i>Revatio® Tablets,</i> <i>Revatio® Oral Suspension,</i> <i>Revatio IV®</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ul style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ul style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC II or III symptoms (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist 5. Member is not concomitantly taking another phosphodiesterase 5 (PDE-5) inhibitor (e.g. tadalafil) 6. Member is not concomitantly taking riociguat (Adempas) 7. Member meets ALL criteria for requested formulation: <ul style="list-style-type: none"> a. Sildenafil citrate tablet, oral suspension (generic) <ul style="list-style-type: none"> i. Dosage does not exceed 20 mg three times a day b. Revatio® Tablets, Revatio® Oral Suspension: <ul style="list-style-type: none"> i. Member has tried and had intolerable adverse effects to generic sildenafil – specific intolerance to generic sildenafil and rationale for use of brand Revatio must be provided in addition to BOTH of the following:

	<ul style="list-style-type: none"> 1. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda 2. Completed Naranjo Adverse Drug reaction probability scale - https://livertox.nih.gov/Naranjoassessment.pdf <ul style="list-style-type: none"> ii. Dosage does not exceed 20 mg three times a day <ul style="list-style-type: none"> c. Revatio IV®: <ul style="list-style-type: none"> i. Member has a contraindication or is temporarily unable to take oral sildenafil citrate therapy ii. Dosage does not exceed 10 mg IV three times a day <p>Approval duration: 1 year</p>
<p>Tadalafil</p> <p><i>Adcirca®;</i></p> <p><i>Alyq™(generic),</i></p> <p><i>Tadliq®</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ul style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ul style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC II or III symptoms (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist 5. Member is not concomitantly taking another phosphodiesterase 5 (PDE-5) inhibitor (e.g. sildenafil citrate) 6. Member is not concomitantly taking riociguat (Adempas) 7. Member has an inadequate response, contraindication, or intolerance to generic sildenafil citrate 8. For brand Adcirca and Tadliq only: Member has tried and had intolerable adverse effects to generic tadalafil or Alyq – specific intolerance to generic tadalafil and rationale for use of brand Adcirca must be provided in addition to BOTH of the following: <ul style="list-style-type: none"> a. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda

	<p>b. Completed Naranjo Adverse Drug reaction probability scale - https://livertox.nih.gov/Naranjoassessment.pdf</p> <p>9. Dosage does not exceed 40 mg daily</p> <p>Approval duration: 1 year</p>
<p>Iloprost inhalation solution</p> <p><i>Ventavis</i>[®]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC III or IV symptoms (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist 5. Member is not concomitantly being treated with another inhaled prostacyclin (e.g. treprostinil inhalation solution) 6. Dosage does not exceed 45 mcg daily (5 mcg 9 times per day) <p>Approval duration: 1 year</p>
<p>Treprostinil inhalation solution and powder</p> <p><i>Tyvaso</i>[®], <i>Tyvaso DPI</i>[®]</p>	<p>Use meets the definition of medical necessity for either of the following indications if ALL criteria are met: the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) <ol style="list-style-type: none"> a. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> i. Right-heart cardiac catheterization ii. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age b. Member exhibits WHO-FC III symptoms (Table 5) c. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) d. Prescribed by a cardiologist or pulmonologist

	<ul style="list-style-type: none"> e. Member is not concomitantly being treated with another inhaled prostacyclin (e.g. iloprost) f. Dosage does not exceed: <ul style="list-style-type: none"> i. Tyvaso inhalation solution: 12 breaths (72 mcg) 4 times daily ii. Tyvaso DPI: 64 mcg 4 times daily <p>2. Treatment of pulmonary hypertension associated with interstitial lung disease (WHO Group 3; Table 4)</p> <ul style="list-style-type: none"> a. Diagnosis is confirmed by either of the following: <ul style="list-style-type: none"> i. Right-heart cardiac catheterization ii. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age b. Member exhibits WHO-FC III symptoms (Table 5) c. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) d. Prescribed by a cardiologist or pulmonologist e. Member is not concomitantly being treated with another inhaled prostacyclin (e.g. iloprost) f. Dosage does not exceed: <ul style="list-style-type: none"> i. Tyvaso inhalation solution: 12 breaths (72 mcg) 4 times daily ii. Tyvaso DPI: 64 mcg 4 times daily <p>Approval duration: 1 year</p>
<p>Treprostinil injection</p> <p><i>Remodulin</i>®</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ul style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ul style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC II-IV symptoms (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin)

	<p>4. Prescribed by a cardiologist or pulmonologist</p> <p>Approval duration: 1 year</p>
<p>Treprostinil oral tablets</p> <p><i>Orenitram™</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC II or III symptoms (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist <p>Approval duration: 1 year</p>
<p>Epoprostenol for IV administration</p> <p><i>Flolan®, Veletri®</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> a. Right-heart catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC III or IV (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist <p>Approval duration: 1 year</p>
<p>Macitentan</p> <p><i>Opsumit®</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC II, III or IV symptoms (Table 5)

	<ol style="list-style-type: none"> 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist 5. Member is not concomitantly taking another endothelin receptor antagonist (e.g. ambrisentan, bosentan) 6. Dosage does not exceed 10 mg daily <p>Approval duration: 1 year</p>
<p>Riociguat <i>Adempas</i>[®]</p>	<p>Use meets the definition of medical necessity for either of the following indications if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) <ol style="list-style-type: none"> a. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> i. Right-heart cardiac catheterization ii. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age b. Member exhibits WHO-FC II, III or IV symptoms (Table 5) c. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) d. Prescribed by a cardiologist or pulmonologist e. Member is not concomitantly taking a phosphodiesterase 5 (PDE-5) inhibitor (e.g. sildenafil citrate, tadalafil) f. Member is not concomitantly taking organic nitrates or nitric oxide donors (e.g., isosorbide mononitrate, isosorbide dinitrate, nitroglycerin) g. Dosage does not exceed 2.5 mg three times daily 2. Treatment of persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4; Table 4) <ol style="list-style-type: none"> a. Diagnosis is confirmed by either of the following: <ol style="list-style-type: none"> i. Right-heart cardiac catheterization ii. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age b. Member has not responded adequately to surgical treatment (e.g., pulmonary endarterectomy) or is not a surgical candidate

	<ul style="list-style-type: none"> c. Prescribed by a cardiologist or pulmonologist d. Member is not concomitantly taking a phosphodiesterase 5 (PDE-5) inhibitor (e.g. sildenafil citrate, tadalafil) e. Member is not concomitantly taking organic nitrates or nitric oxide donors (e.g., isosorbide mononitrate, isosorbide dinitrate, nitroglycerin) f. Dosage does not exceed 2.5 mg three times daily <p>Approval duration: 1 year</p>
<p>Selexipag <i>Uptravi</i>[®]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ul style="list-style-type: none"> 1. Diagnosis is confirmed by either of the following: <ul style="list-style-type: none"> a. Right-heart cardiac catheterization b. Doppler echocardiogram if right heart catheterization cannot be performed AND member is less than 1 year of age 2. Member exhibits WHO-FC II or III symptoms (Table 5) 3. Member has not responded adequately to conventional therapy or is not a candidate for conventional therapy (e.g., calcium channel blockers, diuretics, oxygen therapy, anticoagulants, digoxin) 4. Prescribed by a cardiologist or pulmonologist 5. Member is not concomitantly taking an oral, inhaled, or injectable prostacyclin analog (e.g. epoprostanol, iloprost, treprostinil) 6. Dosage does not exceed 3200 mcg daily <p>Approval duration: 1 year</p>

Table 2

Continuation criteria for use of pulmonary hypertension drug therapy	
Product Brand	Criteria
<p>Ambrisentan <i>Letairis</i>[®]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ul style="list-style-type: none"> 1. Member is not concomitantly taking another endothelin receptor antagonist (e.g. bosentan) 2. Dosage does not exceed 10 mg daily <p>Approval duration: 1 year</p>
<p>Bosentan</p>	<p>Use meets the definition of medical necessity for either of the following indications if ALL criteria are met:</p>

<p><i>Tracleer® tablets, Tracleer® tablets for oral suspension</i></p>	<ol style="list-style-type: none"> 1. Treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) <ol style="list-style-type: none"> a. Member is not concomitantly taking another endothelin receptor antagonist (e.g. ambrisentan) b. Dosage does not exceed 125 mg twice daily 2. Treatment of digital ulcers in patients with systemic sclerosis <p>Approval duration: 1 year</p>
<p><i>Sildenafil citrate Revatio® Tablets, Revatio® Oral Suspension, Revatio IV®</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Member is not concomitantly taking another phosphodiesterase 5 (PDE-5) inhibitor (e.g. tadalafil) 2. Member is not concomitantly taking riociguat (Adempas) 3. Dosage does not exceed: <ol style="list-style-type: none"> a. Sildenafil citrate tablet, oral suspension (generic): 20 mg three times a day b. Revatio® Tablets, Revatio® Oral Suspension: 20 mg three times a day c. Revatio IV®: 10 mg IV three times a day <p>Approval duration: 1 year</p>
<p><i>Tadalafil Adcirca®; Alyq™(generic)</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Member is not concomitantly taking another phosphodiesterase 5 (PDE-5) inhibitor (e.g. sildenafil citrate) 2. Member is not concomitantly taking riociguat (Adempas) 3. Dosage does not exceed 40 mg daily <p>Approval duration: 1 year</p>
<p><i>Iloprost inhalation solution Ventavis®</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Member is not concomitantly being treated with another inhaled prostacyclin (e.g. treprostinil inhalation solution) 2. Dosage does not exceed 45 mcg daily (5 mcg 9 times per day) <p>Approval duration: 1 year</p>
<p><i>Treprostinil inhalation solution and powder Tyvaso®, Tyvaso DPI®</i></p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Member is not concomitantly being treated with another inhaled prostacyclin (e.g. iloprost) 2. Dosage does not exceed: <ol style="list-style-type: none"> a. Tyvaso inhalation solution: 12 breaths (72 mcg) 4 times daily b. Tyvaso DPI: 64 mcg 4 times daily <p>Approval duration: 1 year</p>

<p>Treprostinil injection <i>Remodulin</i>[®]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) Approval duration: 1 year</p>
<p>Treprostinil oral tablets <i>Orenitram</i>[™]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) Approval duration: 1 year</p>
<p>Epoprostenol for IV administration <i>Flofan</i>[®], <i>Veletri</i>[®]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) Approval duration: 1 year</p>
<p>Macitentan <i>Opsumit</i>[®]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Member is not concomitantly taking another endothelin receptor antagonist (e.g. ambrisentan, bosentan) 2. Dosage does not exceed 10 mg daily <p>Approval duration: 1 year</p>
<p>Riociguat <i>Adempas</i>[®]</p>	<p>Use meets the definition of medical necessity for either of the following indications if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) <ol style="list-style-type: none"> a. Member is not concomitantly taking a phosphodiesterase 5 (PDE-5) inhibitor (e.g. sildenafil citrate, tadalafil) b. Member is not concomitantly taking organic nitrates or nitric oxide donors (e.g., isosorbide mononitrate, isosorbide dinitrate, nitroglycerin) c. Dosage does not exceed 2.5 mg three times daily 2. Treatment of persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (WHO Group 4; Table 4) <ol style="list-style-type: none"> a. Member is not concomitantly taking a phosphodiesterase 5 (PDE-5) inhibitor (e.g. sildenafil citrate, tadalafil) b. Member is not concomitantly taking organic nitrates or nitric oxide donors (e.g., isosorbide mononitrate, isosorbide dinitrate, nitroglycerin) c. Dosage does not exceed 2.5 mg three times daily <p>Approval duration: 1 year</p>
<p>Selexipag <i>Uptravi</i>[®]</p>	<p>Use meets the definition of medical necessity for the treatment of pulmonary arterial hypertension (WHO Group 1; Table 4) if ALL criteria are met:</p> <ol style="list-style-type: none"> 1. Member is not concomitantly taking an oral, inhaled, or injectable prostacyclin analog (e.g. epoprostenol, iloprost, treprostinil) 2. Dosage does not exceed 3200 mcg daily <p>Approval duration: 1 year</p>

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Consult product prescribing information for appropriate dosing.

PRECAUTIONS:

Specific precautions and warnings are highlighted in Table 3; however, it is strongly recommended that the prescriber refer to product-specific labeling for complete precautions and warnings.

Table 3

Precautions and warnings of pulmonary hypertension drug therapy	
Product	Precautions/Warnings
Ambrisentan <i>Letairis</i> [®]	Use is contraindicated with organic nitrates. Carefully consider whether underlying conditions (e.g., cardiovascular disease, impaired autonomic control of blood pressure, aortic stenosis) could be adversely affected by vasodilatory effects. Avoid use with CYP3A inhibitors, potent CYP3A inducers, and PDE5 inhibitors.
Bosentan <i>Tracleer</i> [®] tablets, <i>Tracleer</i> [®] tablets for oral suspension	Hepatotoxicity and teratogenicity are associated with use (Boxed Warning). Use with cyclosporine A or glyburide is contraindicated.
Sildenafil citrate <i>Revatio</i> [®] Tablets, <i>Revatio</i> [®] Oral Suspension, <i>Revatio IV</i> [®]	Use is contraindicated with organic nitrates. Carefully consider whether underlying conditions (e.g., cardiovascular disease, impaired autonomic control of blood pressure, aortic stenosis) could be adversely affected by vasodilatory effects.
Tadalafil <i>Adcirca</i> [®] ; <i>Alyq</i> [™] (generic)	Use is contraindicated with organic nitrates. Carefully consider whether underlying conditions (e.g., cardiovascular disease, impaired autonomic control of blood pressure, aortic stenosis) could be adversely affected by vasodilatory effects.
Iloprost inhalation solution <i>Ventavis</i> [®]	Hypotension leading to syncope has been observed with use; do not administer if systolic blood pressure is below 85 mmHg.
Treprostinil inhalation solution and powder <i>Tyvaso</i> [®] , <i>Tyvaso DPI</i> [®]	Use has been associated with increases in bleeding risk, particularly in those receiving anticoagulants.
Treprostinil injection <i>Remodulin</i> [®]	Do not abruptly lower the dose or withdraw dosing.
Treprostinil oral tablets <i>Orenitram</i> [™]	Use is contraindicated in severe hepatic impairment. Do not abruptly discontinue dosing. Use has been associated with increases in bleeding risk, particularly in those receiving anticoagulants.
Epoprostenol <i>Flolan</i> [®] , <i>Velettri</i> [®]	Use is contraindicated in congestive heart failure and pulmonary edema. Do not abruptly lower the dose or withdraw dosing.
Macitentan	Teratogenicity is associated with use (Boxed Warning).

<i>Opsumit</i> [®]	
Riociguat <i>Adempas</i> [®]	Teratogenicity is associated with use (Boxed Warning). Use is contraindicated with nitrates, nitric oxide donors, and PDE inhibitors.
Selexipag Uptravi	Pulmonary edema in patients with pulmonary veno-occlusive disease. If confirmed, discontinue treatment

BILLING/CODING INFORMATION:

HCPCS Coding:

J1325	Injection, epoprostenol, 0.5 mg
J3285	Injection, treprostinil, 1 mg
J3490	Unclassified drugs (Revatio [®] injection)
J7686	Treprostinil, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, 1.74 mg
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified (Tracleer [®] , Letairis [®] , Revatio [®] Tablets, Revatio [®] Oral Solution, sildenafil citrate, Adcirca [®] , Orenitram [™] , Opsumit [®] , Adempas [®] , Uptravi, Tyvaso DPI)
K0455	Infusion pump used for uninterrupted parenteral administration of medication, (e.g., epoprostenol or treprostinil)
K0730	Controlled dose inhalation drug delivery system
Q4074	Iloprost, inhalation solution, FDA-approved final product, non-compound, administered through DME, unit dose form, up to 20 micrograms
S0155	Sterile dilutant for epoprostenol, 50 ml
S9347	Home infusion therapy, uninterrupted, long-term, controlled rate intravenous or subcutaneous infusion therapy (e.g., epoprostenol); administrative services, professional pharmacy services, care coordination and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10 Diagnosis Codes That Support Medical Necessity:

I27.0	Primary pulmonary hypertension
I27.2	Other secondary pulmonary hypertension
I27.89	Other specified pulmonary heart diseases
M34.0	Progressive systemic sclerosis
M34.1	CR(E)ST syndrome
M34.9	Systemic sclerosis, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage Products The following Local Coverage Determination (LCD) was reviewed on the last guideline revised date: L33794 External Infusion Pumps, L33370 Nebulizers located at <http://www.cgsmedicare.com>.

DEFINITIONS:

WHO: World Health Organization

NYHA: New York Heart Association

RELATED GUIDELINES:

None applicable.

OTHER:

Table 4: WHO Clinical Classification of Pulmonary Hypertension

<p>1 PAH</p> <ul style="list-style-type: none">1.1 Idiopathic PAH1.2 Heritable PAH1.3 Drug- and toxin-induced PAH1.4 PAH associated with:<ul style="list-style-type: none">1.4.1 Connective tissue disease1.4.2 HIV infection1.4.3 Portal hypertension1.4.4 Congenital heart disease1.4.5 Schistosomiasis1.5 PAH long-term responders to calcium channel blockers1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement1.7 Persistent PH of the newborn syndrome <p>2 PH due to left heart disease</p> <ul style="list-style-type: none">2.1 PH due to heart failure with preserved LVEF2.2 PH due to heart failure with reduced LVEF2.3 Valvular heart disease2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH <p>3 PH due to lung diseases and/or hypoxia</p> <ul style="list-style-type: none">3.1 Obstructive lung disease3.2 Restrictive lung disease3.3 Other lung disease with mixed restrictive/obstructive pattern

<p>3.4 Hypoxia without lung disease</p> <p>3.5 Developmental lung disorders</p> <p>4 PH due to pulmonary artery obstructions</p> <p>4.1 Chronic thromboembolic PH</p> <p>4.2 Other pulmonary artery obstructions</p> <p>5 PH with unclear and/or multifactorial mechanisms</p> <p>5.1 Haematological disorders</p> <p>5.2 Systemic and metabolic disorders</p> <p>5.3 Others</p> <p>5.4 Complex congenital heart disease</p>
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PAH: pulmonary arterial hypertension; PVOD: pulmonary veno-occlusive disease; PCH: pulmonary capillary haemangiomatosis; LVEF: left ventricular ejection fraction

Table 5: WHO Functional Class (WHO-FC) of Pulmonary Hypertension

WHO-FC	Description
I	Individuals 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.
II	Individuals 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.
III	Individuals 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.
IV	Individuals with pulmonary hypertension with inability to carry out any physical activity without symptoms. These individuals manifest signs of right heart failure. Dyspnea and/or fatigue may be present even at rest. Discomfort is increased by any physical activity.

Table 6: New York Heart Association Functional Classification of Heart Failure

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause symptoms of heart failure (undue fatigue, palpitations, and dyspnea).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of heart failure.
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of heart failure.
IV	Unable to carry out any physical activity without symptoms of heart failure or symptoms of heart failure at rest.

REFERENCES:

1. Actelion Pharmaceuticals. Opsumit (macitentan) tablet, film coated. 2013 [cited 5/20/19]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=1e484a50-55db-4b85-8c57-6cd1b0353abd/>.
2. Actelion Pharmaceuticals. Upravi (selexipag) tablet, coated. 2015 [cited 5/20/19]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a7a23b87-f892-4e2c-8e2e-ebf841220f90>.
3. Barst RJ, Gibbs JS, Ghofrani HA, et al. Updated evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009; 54(1 Suppl):S78-84.
4. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension. *Circulation*. 2012; 125(2):324-34.
5. Bayer HealthCare Pharmaceuticals, Inc. Adempas (riociguat) tablet, film coated. 2013 [cited 5/20/19]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=7b57509a-3d5d-41d4-8fed-1471e26372a3/>.
6. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2022 [cited 7/20/22]. Available from: <http://www.clinicalpharmacology.com/>.
7. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 7/20/22]. Available from: <http://clinicaltrials.gov/>.
8. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 7/20/22].
9. Galie, N., McLaughlin, VV, Rubin, LJ, Simonneau, G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J* 2019; 53: 1802148.
10. McCrory DC, Coeytaux RR, Schmit KM, et al. Pulmonary Arterial Hypertension: Screening, Management, and Treatment. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013 Apr. Report No.: 13-EHC087-EF.
11. 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(16):2250-2294.
12. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2019 [cited 5/20/19]. Available from: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/>.
13. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53:1801913
14. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009; 34(6):1219-63.
15. United Therapeutics Corp. Orenitram (treprostinil) tablet, extended release. 2013 [cited 5/20/19]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=8ed2003a-c801-411e-831e-d06079bb0d7c/>.
16. Yancy CW, Jessup M, Bozkurt B. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;62(16):e147-239.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 8/13/22.

GUIDELINE UPDATE INFORMATION:

11/15/09	New Medical Coverage Guideline.
01/01/10	Annual HCPCS coding update: added HCPCS code Q4074.
07/15/10	Review and revision to guideline; consisting of moving NYHA New York Heart Association Classification to the bullet criteria for coverage. Updated list of conservative therapy drugs. Updated precautions section to include warning regarding concomitant organic nitrate use with PDE-5 inhibitors and enhanced hypotension. Updated PAH classification tables and HCPCS coding section.
01/01/11	Revision; consisting of updating coding.
07/15/11	Review and revision to guideline; consisting of the addition of Revatio IV and WHO Group 1 comment to Flolan/epoprostenol.
07/15/12	Review and revision to guideline; consisting of updates precautions and position statement. Revisions to the position statement for Remodulin to include NYHC II-IV as per prescribing information, updated Flolan, et al to remove specific reference to scleroderma as it is included in the connective tissue disease spectrum for WHO Group I PAH, removed comments regarding improved exercise tolerance.
09/15/12	Revision to guideline; consisting of clarification of continuation criteria.
10/15/12	Revision to guideline; consisting of adding addition criteria for Revatio®.
03/15/13	Revision to guideline; consisting of updating dosage limits for Tracleer, Revatio PO, IV, Adcirca, Ventavis and Tyvaso. Added step for Revatio PO and Adcirca for generic sildenafil citrate preferred. Added therapeutic duplication language for drugs in same class (e.g. Tracleer, Letaris). Added orphan drug designation for Tracleer. Updated Warnings, Updated ICD-9, ICD-10.
07/15/13	Review and revision to guideline; consisting of updating position statement to include generic sildenafil.
03/15/14	Revision to guideline; consisting of revising description, position statement, dosage/administration, precautions/warnings, references.
06/15/14	Revision to guideline; consisting of position statement, precautions/warnings, billing coding, references.
07/15/14	Review and revision to guideline; consisting of description and position statement
08/15/14	Revision to guideline; consisting of position statement.
07/15/15	Review and revision to guideline; consisting of updating references.
11/01/15	Revision: ICD-9 Codes deleted.
03/15/16	Revision; consisting of position statement and precautions/warnings.
07/15/16	Review and revision to guideline; consisting of position statement and coding.
04/01/17	Revision; consisting of position statement.
7/15/17	Review and revision to guideline; consisting of position statement.

11/15/17	Revision to guideline to include new bosentan formulation in position statement, dosing and administration, references.
07/15/18	Review and revision to guideline; consisting of references and position statement.
07/15/19	Review and revision to guideline; consisting of updating references and position statement.
04/01/20	Revision to guideline consisting of changes to position statement.
01/15/21	Revision to guideline consisting of changes to position statement.
09/15/22	Review and revision to guideline; consisting of updating references and position statement.
11/15/22	Updated position statement.