Pharmacy Management Drug Policy

SUBJECT: Pulmonary Hypertension (PH)
POLICY NUMBER: PHARMACY-42
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If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Pulmonary Hypertension is a type of high blood pressure that occurs when the pressure in the blood vessels that carry blood from the heart to the lungs is higher than normal. Patients with pulmonary hypertension are classified into five groups based upon etiology: Group 1 – pulmonary arterial hypertension (PAH); Group 2 – pulmonary hypertension due to left-sided heart disease; Group 3 – due to chronic lung disorders and hypoxia; Group 4 – Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions; Group 5 – pulmonary hypertension due to unclear or multifactorial mechanisms.

Careful invasive assessment of pulmonary hemodynamics is critical in the evaluation of any patient with suspected pulmonary hypertension (PH). All patients that are suspected of having PH after non-invasive evaluation (chest X-ray and echocardiogram) must undergo right heart catheterization (RHC) to confirm the diagnosis, assess severity of disease and guide medication therapy. RHC values distinguish PAH [World Health Organization (WHO) Group 1], PH-ILD (WHO group 3) and CTEPH (WHO Group 4) and from other types of Pulmonary Hypertension (WHO Groups 2, 5) as the pharmacological treatment of these groups is vastly different. RHC can be performed safely even in most pediatric patients and patients with severe pulmonary hypertension.

Interpretation of Right Heart Catheterization hemodynamic values:

Pulmonary Artery Pressure: mPAP

- Normal mean pulmonary artery pressure is typically 11-17mmHg with an upper limit of normal of approximately 20mmHg. When the mPAP is > 20 mmHg this confirms pulmonary hypertension (further testing is necessary to further classify the specific type of pulmonary hypertension / WHO Group **AND** to determine the appropriate medication treatments)

Pulmonary Capillary Wedge Pressure (PCWP)

- Also referred to as pulmonary artery occlusion pressure (PAOP) or pulmonary artery wedge pressure (PAWP) and estimates (is an indirect measurement of) the left atrial pressure.
- Normal pulmonary capillary wedge pressure (PCWP) varies from 6 to 15 mmHg with a mean of 9 mmHg and measures the left atrial pressure.
- In the diagnosis of WHO Group 1 PAH the PCWP remains within normal range ≤ 15 mmHg.
- An elevated PCWP > 15 mm Hg is not consistent with a diagnosis of WHO Group 1 PAH.

- Conditions that raise left ventricular end-diastolic pressure result in an elevated wedge pressure (> 15 mm Hg) including left ventricular systolic heart failure, left ventricular diastolic heart failure, mitral and aortic valve disease, hypertrophic cardiomyopathy; hypervolemia, right-to-left shunts, cardiac tamponade, and constrictive and restrictive cardiomyopathies.

Pulmonary Vascular Resistance (PVR)

- A measure of the pulmonary blood vessel resistance to blood flow
- Calculated from RHC hemodynamic values including mPAP, pulmonary capillary wedge pressure and cardiac output.
- PVR (wood units) = $\frac{\text{mPAP} - \text{PCWP (mmHg)}}{\text{CO (L/min)}}$
- Pulmonary vascular resistance may be reported in dynes/sec/cm^5. To convert this measurement to wood units, divide by 80.
- For reference a calculator is found at www.easycalculation.com/medical/pulmonary.php Divide result by 80 for wood units.

Group 1 - Pulmonary arterial hypertension (PAH) is a type of pulmonary hypertension characterized by sustained elevation of pulmonary artery pressure. The condition is uncommon but is associated with a high mortality rate. Some causes of and risk factors for pulmonary arterial hypertension include congenital heart defects, connective tissue disease (scleroderma), HIV infection, blood clots, liver disease (portal hypertension) and medication (ex. Fen-phen). The disease can also have an unknown cause: idiopathic pulmonary arterial hypertension (PAH). The most common symptoms caused by PAH are unusual fatigue, shortness of breath, chest pain, fainting, and peripheral edema.

Group 2 - Pulmonary hypertension due to left heart disease (PH-LHD) is the most common cause of pulmonary hypertension. Patients with PH-LHD typically present with symptoms and signs related to HF such as dyspnea, fatigue, and signs of pulmonary and/or peripheral edema. Characterized by pulmonary hypertension associated with an elevated left atrial pressure (e.g., mean LA pressure >14 mmHg) resulting in pulmonary venous hypertension (i.e., post-capillary PH). Defined hemodynamically as a mean pulmonary arterial pressure (mPAP) > 20 mmHg and a PCWP > 15 mmHg and normal or reduced cardiac output. Targeted PAH medications (contained within this policy) are not indicated for routine use in PH-LHD. The proceedings of the 6th World Symposium on Pulmonary Hypertension include a strong recommendation against use of PH-targeted therapies in this clinical setting. Further study is required to determine the safety and efficacy of these agents in patients with PH-LHD.

Group 3 - Patients with pulmonary hypertension (PH) due to diffuse lung disease (e.g., chronic obstructive pulmonary disease, interstitial lung disease, or overlap syndromes) or conditions that cause hypoxemia (e.g., obstructive sleep apnea, alveolar hypoventilation disorders) are classified as having group 3 PH. Interstitial Lung disease includes several conditions characterized by scarring (fibrosis) within the lungs such as Idiopathic pulmonary fibrosis (IPF), connective tissue diseases (CTDs), combined pulmonary fibrosis and emphysema (CPFE) and Lymphangioleiomyomatosis (LAM). Pulmonary hypertension frequently complicates the course of patients with ILD (PH-ILD) and is associated with worse functional status measured by exercise capacity, greater supplemental oxygen needs, decreased quality of life, and worse outcomes.

Group 4 - Chronic thromboembolic pulmonary hypertension (CTEPH) is a complication of pulmonary embolism and a major cause of pulmonary hypertension which can lead to right heart failure and death. Common symptoms include dyspnea on exertion, rapid exhaustion, and fatigue. Lung ventilation/perfusion (V/Q scan) is the preferred and recommended screening test. Surgery is the only

definitive therapy for CTEPH, with pulmonary thromboendarterectomy (PTE) being the surgical procedure of choice.

Group 5 - Pulmonary hypertension due to unidentified / multifactorial mechanisms includes patients with PH who do not clearly fit into group 1 through 4 pulmonary hypertensions. Contributing diagnoses for PH in this group include those with hematologic disorders such as chronic hemolytic anemia, myeloproliferative disorders, systemic or metabolic disorders including sarcoidosis, pulmonary Langerhans histiocytosis X, neurofibromatosis, Gaucher disease, glycogen storage disease, complex congenital heart disorders except patients with PH due to corrected or uncorrected left to right intracardiac or extracardiac shunts and others including chronic kidney disease or fibrosing mediastinitis.

Treatment goals include improvement in both short-term functional symptoms as well as long-term outcomes such as: dyspnea and exercise endurance, lowering pulmonary artery pressure, reduce hospitalizations, prevent progression of disease, and improve survival.

Medical management addressed in this policy includes the following advanced therapies: endothelial-receptor antagonists (bosentan, ambrisentan, macitentan), phosphodiesterase-5 inhibitors (sildenafil, tadalafil) and prostacyclins (iloprost, treprostinil, epoprostenol) and the newer classes of sGC inhibitors (riociguat) and prostacyclin IP receptor agonists (selexipag).

(See appendix for Pulmonary Hypertension WHO and Clinical Classification, Hemodynamic classifications of pre- and post-capillary pulmonary hypertension, NYHA Functional Classification and WHO Pulmonary Hypertension Functional Classification).

DRUG SPECIFIC POLICIES / CRITERIA:

Adcirca, generic tadalafil (including Alyq*), Tadliq – Pharmacy benefit
Tadalafil is a phosphodiesterase-5 enzyme inhibitor (PDE5) indicated for treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group 1) to improve exercise ability. *Please note: Alyq is an FDA-approved generic equivalent to Adcirca; therefore, requests for Alyq will follow the requirements for tadalafil throughout this policy. Where tadalafil is mentioned the use of Alyq will be accepted to satisfy that requirement. 1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND** 2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND** 3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting: • Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND** • Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND** • Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND** 4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND** 5. Adcirca and equivalent generic tadalafil will not be authorized for a diagnosis of erectile dysfunction as there are FDA approved medications for this diagnosis, **AND** 6. Requests for brand name Adcirca will require documentation of serious side effects or drug failure with the equivalent generic tadalafil product indicated for a diagnosis of PAH Dosing guidelines: a. Adcirca, Alyq and generic tadalafil tablet: 40mg orally once daily. b. Tadliq: 40mg (10mL) once daily. Quantity limit: 300 milliliters per 30-day supply.

See "Combination Therapy" below for recommendations regarding the use of tadalafil and ambrisentan.

Adempas (riociguat) – Pharmacy benefit

Adempas (riociguat): is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with:

- Pulmonary arterial hypertension (PAH) (WHO group 1) to improve exercise capacity, improve WHO functional class, and delay clinical worsening.
- Persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) (World Health Organization [WHO] group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class.

Drug Criteria for Pulmonary Arterial Hypertension (PAH):

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must be at least 18 years of age, **AND**
3. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
4. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
   - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
   - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
   - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
5. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
6. Step therapy applies – must have an adequate trial of at least one of the following oral generic *preferred* products with evidence of severe intolerance or drug failure / disease progression despite these treatments:
   a. PDE5 inhibitor: sildenafil or tadalafil
   b. ERA: ambrisentan, bosentan

Drug Criteria for chronic thromboembolic pulmonary hypertension (CTEPH):

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of CTEPH; **AND**
2. Must be at least 18 years of age, **AND**
3. Must have a diagnosis of World Health Organization (WHO) Group 4 CTEPH; **AND**
4. The diagnosis must be confirmed by Right Heart Catheterization (RHC) **AND** ventilation/perfusion scintigraphy (V/Q scan) or pulmonary angiogram (or both); **AND**
5. Right Heart Catheterization must confirm the diagnosis of pulmonary hypertension:
   - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
   - Pulmonary capillary wedge pressure (PCWP) ≤ to 15 mm Hg at rest; **AND**
   - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU); **AND**
6. The patient must have recurrent or persistent disease after surgical intervention **OR**
7. Inoperable disease determined by V/Q scan and/or pulmonary angiography in consultation with an experienced pulmonary thromboendarterectomy center.
8. Progress notes including relevant diagnostic test results (including Right Heart Catheterization **AND** V/Q scan or pulmonary angiography) are required.
9. Requests for the use of Adempas as a bridge to surgery/surgical evaluation requires submission of provider rationale for this use, a medical / surgical treatment plan and will be considered on a case-by-case basis. Adempas will *not* be approved as a replacement for surgery in patients who are deemed operable, since surgical intervention is the only curative treatment for CTEPH at this time.

a. Any approvals for use as a bridge-to-surgery/surgical evaluation will be short-term and limited to the timeframe needed for the surgical evaluation/surgical intervention and post-surgical evaluation to occur per the treatment plan.
b. Requests for recertification / continued coverage as a bridge-to-surgery/surgical evaluation will be reviewed with policy criteria found in 9 above.
c. After surgery/surgical evaluation has occurred, requests for continued coverage of Adempas will be evaluated based on criteria 1-8 above.

Dosing guidelines:

a. Maximum dose of Adempas (riociguat) is 2.5mg three times a day,
b. Of note: active smokers may require a titration above this based on increased drug metabolism. A dose decrease may be required in patients who stop smoking

Flolan, Veletri, and generic epoprostenol – Medical benefit

Prostacyclins (including epoprostenol) are generally not recommended as first- or second-line PAH treatments according to the 6th World Symposium on Pulmonary Hypertension and updated CHEST (American College of Chest Physicians) guidelines except in certain clinical scenarios noted below.

Epoprostenol is a prostacyclin vasodilator indicated for treatment of pulmonary arterial hypertension (PAH) (World Health Organization group 1) to improve exercise capacity.

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
   - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
   - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
   - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
5. Commercial, Exchange and SafetyNet (Medicaid Managed Care, HARP, CHP, Essential Plan) lines of business: Requests for brand name Flolan or brand name Veletri, for NEW STARTS, **AND** EXISTING USERS at the time of recertification, will require documentation of serious side effects or drug failure with generic epoprostenol.
   Medicare lines of business: Requests for brand name Flolan or brand name Veletri, for NEW STARTS ONLY, will require documentation of serious side effects or drug failure with generic epoprostenol, **AND**
6. Must have had had an adequate trial of **TWO,** standard of care, oral therapies from two different classes (a, b or c) alone or in combination with evidence of unacceptable or deteriorating clinical status despite these treatments:
   a. PDE5 inhibitor: sildenafil or tadalafil
   b. ERA: ambrisentan, bosentan or Opsumit
   c. Adempas (riociguat); **AND**
7. Past treatment with a prostacyclin (Flolan, Veletri, epoprostenol, Tyvaso, Remodulin, treprostinil or Ventavis) will also be taken into consideration if used as one of two previous therapies
8. Patients with World Health Organization Functional Class (WHO-FC) III symptoms and evidence of rapidly progressing disease or other markers of poor clinical prognosis may require treatment with IV/SC or inhaled prostacyclin as initial or secondary therapy, **OR**

9. Patients with World Health Organization Functional Class (WHO-FC) IV symptoms may require continuous treatment with IV/SC prostacyclin as initial therapy according to treatment guidelines from the 6th World Symposium on Pulmonary Hypertension (WSPH).
   (IV prostacyclins include: Flolan/Veletri/epoprostenol and Remodulin/treprostinil)
   (SC prostacyclins include: Remodulin/treprostinil)

Letairis and generic ambrisentan – Pharmacy benefit

Ambrisentan is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group 1):

- To improve exercise ability and delay clinical worsening.
- In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
   - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
   - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
   - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
5. Requests for <u>brand name Letairis</u> will require documentation of serious side effects or drug failure with generic ambrisentan.

Dosing guidelines:

a. The maximum dose of Letairis / generic ambrisentan is 10mg once a day
b. Initiating therapy in combination with ambrisentan has been shown to be beneficial. See "Combination Therapy" below for recommendations regarding the use of ambrisentan and tadalafil as initial oral advanced therapy

Opsumit (macitentan) – Pharmacy benefit

Opsumit (macitentan): is an endothelin receptor antagonist (ERA) indicated for treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group 1) to reduce the risks of disease progression and hospitalization for PAH.

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must be at least 18 years of age, **AND**
3. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
4. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
   - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
   - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
   - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
5. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**

6. Step therapy applies – must have an adequate trial of at least one of the following oral *preferred* generic products with evidence of severe intolerance or drug failure / disease progression despite these treatments:
    a. PDE5 inhibitor: sildenafil or tadalafil
    b. ERA: ambrisentan, bosentan

Dosing guidelines:
    a. Maximum dose of Opsumit (macitentan) is 10mg once a day. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended

Orenitram (treprostinil) – Pharmacy benefit

Orenitram is not recommended as a first- or second-line PAH treatment according to the 6th World Symposium on Pulmonary Hypertension and updated CHEST (American College of Chest Physicians) guidelines.

Orenitram (treprostinil): is a prostacyclin vasodilator indicated for Treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group 1) to delay disease progression and to improve exercise capacity.

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
5. Must have had an adequate trial of TWO oral therapies from two different classes (a, b, or c) alone or in combination or have evidence of severe intolerance or rapid disease progression despite these treatments:
    i. PDE5 inhibitor: sildenafil or tadalafil
    ii. ERA: ambrisentan, bosentan or Opsumit
    iii. Adempas (riociguat), **AND**
6. Past treatment with a prostacyclin (Flolan, Veletri, epoprostenol, Tyvaso, Remodulin, treprostinil or Ventavis) will also be taken into consideration if used as one of two previous therapies

Dosing guidelines:
    a. 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 to the highest tolerated dose. Orenitram titration may be initiated with Orenitram Titration Kits or Orenitram tablets with appropriate titration schedule.
    b. There is no FDA approved maximum dose of oral Orenitram (treprostinil), but the maximum dose allowed within the clinical trials was 16mg twice a day.

Remodulin and generic treprostinil – Medical Benefit

Prostacyclins (including treprostinil) are generally not recommended as first- or second-line PAH treatments according to the 6th World Symposium on Pulmonary Hypertension and updated CHEST (American College of Chest Physicians) guidelines except in certain clinical scenarios noted below.

Treprostinil is a prostacyclin vasodilator indicated for Treatment of pulmonary arterial hypertension (PAH) (World Health Organization group 1) in patients with New York Health Association Class II to IV symptoms to decrease exercise-associated symptoms; to diminish clinical deterioration when transitioning from epoprostenol

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
5. Commercial, Exchange and SafetyNet (Medicaid Managed Care, HARP, CHP, Essential Plan) lines of business: Requests for brand name Remodulin, for NEW STARTS **AND** EXISTING USERS at the time of recertification, will require documentation of serious side effects or drug failure with generic treprostinil.
   Medicare lines of business: Requests for brand name Remodulin, for NEW STARTS ONLY, will require documentation of serious side effects or drug failure with generic treprostinil, **AND**
6. Must have had had an adequate trial of TWO oral therapies from two different classes (a, b, or c) alone or in combination with evidence of unacceptable or deteriorating clinical status despite these treatments:
    a. PDE5 inhibitor: sildenafil or tadalafil
    b. ERA: ambrisentan, bosentan or Opsumit
    c. Adempas (riociguat); **AND**
7. Past treatment with a prostacyclin (Flolan, Veletri, epoprostenol, Tyvaso, Remodulin, treprostinil or Ventavis) will also be taken into consideration if used as one of two previous therapies
8. Patients with World Health Organization Functional Class (WHO-FC) III symptoms and evidence of rapidly progressing disease or other markers of poor clinical prognosis may require treatment with IV/SC or inhaled prostacyclin as initial or secondary therapy, **OR**
9. Patients with World Health Organization Functional Class (WHO-FC) IV symptoms may require continuous treatment with IV/SC prostacyclin as initial therapy according to treatment guidelines from the 6th World Symposium on Pulmonary Hypertension (WSPH). (IV prostacyclins include: Flolan/Veletri/epoprostenol and Remodulin/treprostinil) (SC prostacyclins include: Remodulin/treprostinil)

Revatio / Liqrev / generic sildenafil – Pharmacy benefit

Sildenafil is a phosphodiesterase-5 enzyme inhibitor (PDE5) indicated for treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group 1):

- in adults to improve exercise ability and delay clinical worsening, and
- in pediatric patients 1 to 17 years old to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required on all new and recertification requests, **AND**
5. Revatio and equivalent generic sildenafil will not be authorized for a diagnosis of erectile dysfunction as there are FDA approved medications for this diagnosis, **AND**
6. Requests for <u>brand name Revatio</u> will require documentation of serious side effects or drug failure with the equivalent generic sildenafil product indicated for a diagnosis of PAH.
7. Requests for brand name Liqrev suspension, Revatio suspension and sildenafil suspension will require:
    - Patient must be < 18 years of age, **OR**
    - For patients 18 years of age and older, there must be documentation of an inability to swallow whole tablets with documentation of inability to swallow provided

Dosing guidelines:

a. Adults: The recommended dosage of sildenafil is 20mg 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
b. Pediatric patients dosed by body weight as follows:
    - ≤20 kg the recommended dosage is 10 mg three times a day
    - 20 kg to 45 kg, the recommended dosage is 20 mg three times a day
    - 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

Tracleer / generic bosentan – Pharmacy Benefit

Bosentan is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] group 1)

- in adults to improve exercise ability and to decrease clinical worsening. **AND**
- in pediatric patients ≥3 years of age with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR) which is expected to result in an improvement in exercise ability

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must be at least 3 years of age, **AND**
3. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
4. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**

5. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required on all new and recertification requests, **AND**
6. Requests for brand name Tracleer will require documentation of severe intolerance or therapeutic failure with generic bosentan. **Exceptions are permitted for patients < 12 years of age **AND** weighing < 40kg for which the recommended product strength is not generically available at this time, **AND**
7. Member's current weight with date of measurement and requested dose regimen must be submitted with all new and recertification requests, **AND**
8. Quantity limit of Tracleer 32mg is 30 tablets / 30 days. Quantity limit for generic bosentan/Tracleer 62.5mg and 125mg is 60 tablets / 30 days.
    a. Upon each drug review and dose escalation request, the allowed quantity will be reviewed in accordance with the FDA-approved weight-based dosing (see Table 1 below) and, as such, will be limited to the minimum number of oral tablets or tablets for oral suspension (dispersible tablets) of each strength to obtain the appropriate daily dose.

Dosing guidelines:

a. Maximum dose of Tracleer / bosentan is 125mg twice a day. Doses above 125 mg twice daily did not appear to confer additional benefit sufficient to offset the increased risk of hepatotoxicity.

Table 1 – FDA-approved weight-based dosing

Member age	Member weight (kg)	FDA approved dose regimen	Covered product	Quantity per 30-day supply permitted upon review
3-12 years	4 to 8 kg	16 mg orally twice daily	Tracleer 32mg tablet	30
3-12 years	Greater than 8kg up to 16kg	32mg orally twice daily	Tracleer 32mg tablet	60
3-12 years	Greater than 16kg up to 24kg	48mg orally twice daily	Tracleer 32mg tablet	90
3-12 years	Greater than 24kg up to 40kg	64mg orally twice daily	Tracleer 32mg tablet	120
Older than 12 years	Less than 40kg	62.5mg orally twice daily	Bosentan 62.5mg tablet	60
Older than 12 years	Greater than 40kg	Initial 62.5mg twice daily for 4 weeks …	Bosentan 62.5mg tablet	60
"	"	Then increase to maintenance dose of 125mg orally twice daily	Bosentan 125mg tablet	60

Tyvaso (treprostinil) inhalation, Tyvaso DPI – Pharmacy Benefit

Tyvaso (treprostinil) inhalation is a prostacyclin indicated for the treatment of:

- Pulmonary arterial hypertension (World Health Organization [WHO] group 1) in patients with NYHA Class III symptoms to improve exercise ability
- Pulmonary hypertension associated with interstitial lung disease (WHO Group 3) to improve exercise ability.

Drug Criteria for Pulmonary Arterial Hypertension (PAH):

Prostacyclins are generally not recommended as first- or second-line PAH treatments according to the 6th World Symposium on Pulmonary Hypertension and updated CHEST (American College of Chest Physicians) guidelines except in certain clinical scenarios noted below.

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
5. Must have had an adequate trial of TWO oral therapies from two different classes (a, b, or c) alone or in combination with evidence of unacceptable or deteriorating clinical status despite these treatments:
    a. PDE5 inhibitor: sildenafil or tadalafil
    b. ERA: ambrisentan, bosentan or Opsumit
    c. Adempas (riociguat); **AND**
6. Past treatment with a prostacyclin (Flolan, Veletri, epoprostenol, Remodulin, treprostinil or Ventavis) will also be taken into consideration if used as one of two previous therapies: **OR**
7. Patients with World Health Organization Functional Class (WHO-FC) III symptoms and evidence of rapidly progressing disease or other markers of poor clinical prognosis may require treatment with IV/SC or inhaled prostacyclin as initial or secondary therapy.

Dosing guidelines:

a. Tyvaso inhalation solution: Studies evaluating effectiveness used a target dose of 54 mcg (9 inhalations) four times per day.
b. Tyvaso DPI: Target dose of 48 to 64 mcg inhaled per session, four times per day
Please note: Tyvaso DPI Titration Kits are intended for new patients titrating to their target maintenance dose. Once patients are on a stable target maintenance dose, they should be transitioned to a maintenance kit product.

Drug Criteria for Pulmonary hypertension associated with interstitial lung disease [PH-ILD, World Health Organization (WHO) group III]

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of pulmonary hypertension and chronic lung disorders, **AND**
2. Must be at least 18 years of age, **AND**
3. Must have a diagnosis of WHO group 3 pulmonary hypertension associated with interstitial lung disease [such as idiopathic pulmonary fibrosis (IPF), idiopathic interstitial pneumonia, WHO group 3 connective tissue disease, chronic hypersensitivity pneumonitis, combined pulmonary fibrosis and emphysema (CPFE)], **AND**
4. Right heart catheterization confirms pulmonary hypertension in the setting of chronic lung disease (documentation required):
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
5. Baseline pulmonary function test results confirming moderate to severely impaired lung disease including Forced Vital Capacity < 70%, **AND**
6. High-resolution CT scan finding characteristic airway and/or parenchymal abnormalities associated with interstitial lung disease, **AND**

7. Must have clinical symptoms associated with PH-ILD such as shortness of breath with exertion that is not fully explained by the severity of lung disease, decreased exercise capacity, labored breathing, fatigue, lethargy **AND**
8. Baseline 6-minute walk test to assess disease severity and clinical response to treatment, **AND**
9. Baseline NT-proBNP [N-terminal pro–B-type natriuretic peptide] level, **AND**
10. Progress notes are required to be submitted with requests for initial coverage and existing users,
11. Initial approval will be for 6 months
12. Recertification will require documentation of stabilization or improvement in 6MWT from baseline, decrease in NT-proBNP levels as well as stabilization or reduction in disease severity such as improvements in FVC, reduction in exacerbations of the underling lung disease and clinical worsening.

Dosing guidelines:

a. Tyvaso Inhalation Solution: Studies establishing effectiveness used a target dose of 72 mcg (12 inhalations) four times per day
b. Tyvaso DPI: Target dose of 48 to 64 mcg inhaled per session, four times per day.
Please note: Tyvaso DPI Titration Kits are intended for new patients titrating to their target maintenance dose. Once patients are on a stable target maintenance dose, they should be transitioned to a maintenance kit product.

Uptravi (selexipag) – Pharmacy benefit

Uptravi is not recommended as first- or second-line PAH treatments according to the 6th World Symposium on Pulmonary Hypertension and updated CHEST (American College of Chest Physicians) guidelines.

Uptravi (selexipag): is a prostacyclin receptor agonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must be at least 18 years of age, **AND**
3. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
4. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
5. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
6. Must have had an adequate trial of TWO oral therapies from two different classes (a, b, or c) alone or in combination or has evidence of severe intolerance or rapid disease progression despite these treatments:
    a. PDE5 inhibitor: sildenafil or tadalafil
    b. ERA: ambrisentan, bosentan or Opsumit
    c. Adempas (riociguat), **AND**
7. Past treatment with a prostacyclin (Flolan, Veletri, epoprostenol, Tyvaso, Remodulin, treprostinil or Ventavis) will also be taken into consideration if used as one of two previous therapies, **AND**

8. UPTRAVI TABLETS - The initial approval for Uptravi will be for 6 months to allow for dose titration. If after the initial 6-month approval the dose is still being titrated then an additional 6 months will be authorized, **AND**
9. Subsequent requests for UPTRAVI TABLETS will be evaluated yearly for dose efficiency (i.e., a dose of 800mcg will require the use of 800mcg tablets in lieu of combining lower strength tablets to achieve the same dose.).
10. UPTRAVI for INJECTION – Indicated for patients who are temporarily unable to take oral therapy.
    i. Uptravi for injection will be covered under the member's *medical benefit.*
    ii. Uptravi for injection is administered twice daily by IV infusion at a dose that corresponds to the patient's current dose of Uptravi tablets (please refer to the FDA approved package labelling for the equivalent IV dosage).
    iii. Approval will be for 1 month.
    iv. Recertification requires documentation of continued medical necessity of Uptravi for injection and inability to take oral therapy.

Dosing guidelines:

a. Maximum dosing of Uptravi (selexipag) tablets is 1,600 mcg twice daily
b. Maximum dosing of Uptravi (selexipag) IV infusion is 1800 mcg (equivalent to 1600 mcg oral dose) twice daily.

Ventavis (iloprost) inhalation – Medical benefit

Prostacyclins are generally not recommended as first- or second-line PAH treatments according to the 6th World Symposium on Pulmonary Hypertension and updated CHEST (American College of Chest Physicians) guidelines except in certain clinical scenarios noted below.

Iloprost is a prostacyclin mimetic 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.

1. Must be prescribed by a cardiologist or pulmonologist experienced in the treatment of Pulmonary Arterial Hypertension (PAH), **AND**
2. Must have a diagnosis of World Health Organization (WHO) Group 1 Pulmonary Arterial Hypertension (PAH), **AND**
3. The diagnosis of PAH must be confirmed by Right Heart Catheterization (RHC) documenting:
    - Mean pulmonary artery pressure (mPAP) of > 20 mmHg at rest **AND**
    - Pulmonary capillary wedge pressure (PCWP) ≤ 15 mm Hg at rest **AND**
    - Pulmonary Vascular Resistance (PVR) > 2 wood units (WU), **AND**
4. Progress notes including relevant diagnostic test results (including Right Heart Catheterization report clearly documenting mPAP, PCWP and PVR) are required for all requests, **AND**
5. Must have had an adequate trial of TWO oral therapies from two different classes (a, b, or c) alone or in combination with evidence of unacceptable or deteriorating clinical status despite these treatments:
    a. PDE5 inhibitor: sildenafil or tadalafil
    b. ERA: ambrisentan, bosentan or Opsumit
    c. Adempas (riociguat); **AND**
6. Past treatment with a prostacyclin (Flolan, Veletri, epoprostenol, Tyvaso, Remodulin, treprostinil or Ventavis) will also be taken into consideration if used as one of two previous therapies: **OR**
7. Patients with World Health Organization Functional Class (WHO-FC) III symptoms and evidence of rapidly progressing disease or other markers of poor clinical prognosis may require treatment with IV/SC or inhaled prostacyclin as initial or secondary therapy

Dosing guidelines: a. Maximum dose is 45 mcg/day (5 mcg per dose 9 times per day)
Combination therapy
Ambrisentan and tadalafil - Combination therapy: • In October 2015, the FDA approved the combination of Letairis / ambrisentan in combination with Adcirca / tadalafil to treat patients with PAH (WHO Group 1) to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability. This approval was based on the results of the Ambition trial in which participants were started on combination therapy as initial treatment and demonstrated less clinical failure than those that were started on monotherapy of either drug. Based on this, a combination regimen of tadalafil and ambrisentan will be authorized as initial advanced therapy for those with a confirmed diagnosis of WHO Group 1 PAH. • Alternative combination regimens: Other combination therapy regimens (combining drugs with different mechanisms of action) have been studied for the treatment of PAH with mixed results (such as macitentan + sildenafil; riociguat + bosentan, tadalafil + bosentan). The goal of combination therapy should be to maximize efficacy, while minimizing toxicity. For WHO Functional Class III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, alternative combination therapy regimens can be considered. Combination therapy should only be attempted by those with the expertise to monitor such high-risk individuals.

APPROVAL TIME PERIODS:

Line of Business	Pharmacy benefit Initial approval	Pharmacy benefit Continued approval	Medical Benefit Initial approval	Medical Benefit Continued Approval
Commercial, Exchange and SafetyNet (Medicaid, HARP, CHP, Essential Plan)	2 years *Does not apply to Medicaid and HARP	2 years *Does not apply to Medicaid and HARP	All sites of service: 2 years	All sites of service: 2 years
Medicare	Defined in Medicare Drug Policy	Defined in Medicare Drug Policy	All sites of service: 2 years	All sites of service: 2 years

POLICY GUIDELINES:

1. Unless otherwise stated within the individual drug criteria, approval time periods are listed in the table above.
    - Continued approval at time of recertification will require documentation that the drug is providing ongoing benefit to the patient in terms of improvement or stability in disease state or condition. Such documentation may include progress notes, imaging or laboratory findings, and other objective or subjective measures of benefit which support that continued use of the requested product is medically necessary. Also, ongoing use of the requested product must continue to reflect the current policy's preferred formulary [Recertification reviews may result in the requirement to try more cost-effective treatment alternatives as they become available (i.e., generics or other guideline-supported treatment options)] and the requested dose must continue to meet FDA approved or off-label/guideline supported dosing
2. Utilization Management are contract dependent and coverage criteria may be dependent on the contract renewal date. Additionally, coverage of drugs listed in this policy are contract dependent. Refer to specific contract/benefit language for exclusions.
3. For contracts where Insurance Law § 4903(c-1), and Public Health Law § 4903(3-a) are

applicable, if trial of *preferred* drug(s) is the only criterion that is not met for a given condition, and one of the following circumstances can be substantiated by the requesting provider, with medical rationale **AND** supporting documentation, then trial of the *preferred* drug(s) will not be required.

- The required prescription drug(s) is (are) contraindicated or will likely cause an adverse reaction or physical or mental harm to the member.
- The required prescription drug is expected to be ineffective based on the known clinical history and conditions and concurrent drug regimen.
- The required prescription drug(s) was (were) previously tried while under the current or a previous health plan, or another prescription drug or drugs in the same pharmacologic class or with the same mechanism of action was (were) previously tried and such prescription drug(s) was (were) discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse event.
- The required prescription drug(s) is (are) not in the patient's best interest because it will likely cause a significant barrier to adherence to or compliance with the plan of care, will likely worsen a comorbid condition, or will likely decrease the ability to achieve or maintain reasonable functional ability in performing daily activities.
- The individual is stable on the requested prescription drug. The medical profile of the individual (age, disease state, comorbidities), along with the rational for deeming stability as it relates to standard medical practice and evidence-based practice protocols for the disease state will be taken into consideration.

4. The above criteria are not applicable to requests for brand name medications that have an AB rated generic. We can require a trial of an AB-rated generic equivalent prior to providing coverage for the equivalent brand name prescription drug
5. This policy is applicable to drugs that are included on a specific drug formulary (RX benefit only). If a drug referenced in this policy is non-formulary, please reference the Coverage Exception Evaluation Policy for All Lines of Business Formularies policy for review guidelines.
6. Supportive documentation of previous drug use must be submitted for any criteria that require a trial of a preferred agent, if the preferred drug is not found in claims history.
7. Dose and frequency should be in accordance with the FDA label or recognized compendia (for off label uses). When services are performed in excess of established parameters, they may be subject to review for medical necessity.

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. Codes may not be covered under all circumstances. Please read the policy and guidelines statements carefully

Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I), Not medically necessary / appropriate = (NMN).

HCPCS	
J1325	Flolan, Veletri, generic epoprostenol
J3285	Remodulin, generic treprostinil
J7686	Tyvaso (treprostinil, inhalation solution)
Q4074	Ventavis (iloprost, inhalation)

Appendix A:

Pulmonary Hypertension (PH) WHO Classification	
Group 1	PAH (pulmonary arterial hypertension)
Group 2	PH due to left heart disease
Group 3	PH due to lung disease and/or hypoxemia
Group 4	PH due to pulmonary artery obstructions; CTEPH (chronic thromboembolic pulmonary hypertension)
Group 5	PH due to unclear multifactorial mechanisms

Clinical classification of pulmonary hypertension

- **GROUP 1** Pulmonary arterial hypertension (PAH)
  - 1.1 Idiopathic
    - 1.1.1 Non-responders at vasoreactivity testing
    - 1.1.2 Acute responders at vasoreactivity testing
  - 1.2 Heritable
  - 1.3 Associated with drugs and toxins
  - 1.4 Associated with:
    - 1.4.1 Connective tissue disease
    - 1.4.2 HIV infection
    - 1.4.3 Portal hypertension
    - 1.4.4 Congenital heart disease
    - 1.4.5 Schistosomiasis
  - 1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
  - 1.6 Persistent PH of the newborn
- **GROUP 2** PH associated with left heart disease
  - 2.1 Heart failure:
    - 2.1.1 with preserved ejection fraction
    - 2.1.2 with reduced or mildly reduced ejection fraction
  - 2.2 Valvular heart disease
  - 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
- **GROUP 3** PH associated with lung diseases and/or hypoxia
  - 3.1 Obstructive lung disease or emphysema
  - 3.2 Restrictive lung disease
  - 3.3 Lung disease with mixed restrictive/obstructive pattern
  - 3.4 Hypoventilation syndromes
  - 3.5 Hypoxia without lung disease (e.g. high altitude)
  - 3.6 Developmental lung disorders
- **GROUP 4** PH associated with pulmonary artery obstructions
  - 4.1 Chronic thrombo-embolic PH
  - 4.2 Other pulmonary artery obstructions
- **GROUP 5** PH with unclear and/or multifactorial mechanisms
  - 5.1 Haematological disorders
  - 5.2 Systemic disorders
  - 5.3 Metabolic disorders
  - 5.4 Chronic renal failure with or without haemodialysis
  - 5.5 Pulmonary tumour thrombotic microangiopathy
  - 5.6 Fibrosing mediastinitis

PAH: pulmonary arterial hypertension
PVOD: pulmonary veno-occlusive disease
PCH: pulmonary capillary hemangiomatosis
PH: pulmonary hypertension
LVEF: left ventricular ejection fraction

Hemodynamic definitions of pre- and post-capillary pulmonary hypertension

Definitions	Characteristics	Typical Clinical groups (see list above)
Pulmonary hypertension (PH)	mPAP > 20 mm Hg	All
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR > 2 WU	Pulmonary arterial hypertension PH attributable to lung disease CTEPH
Combined pre- and post-capillary PH (CpcPH)	mPAP > 20 mm Hg PVR > 2 WU PAWP > 15 mm Hg	Left heart disease Left heart + lung disease overlap
Isolated post-capillary PH (IpcPH)	mPAP >20 mmHg PVR ≤ 2 WU	Left heart disease
Exercise PH	mPAP/CO slope between rest and exercise > 3 mm Hg/L per min	Exertional dyspnea with preserved LV ejection fraction with normal resting PAWP

Appendix B:

New York Heart Association Functional Classification	
Class 1	Ordinary physical activity does not cause symptoms
Class 2	Comfortable at rest, ordinary physical activity causes symptoms
Class 3	Comfortable at rest, less than ordinary activity (ADLs) causes symptoms
Class 4	Symptoms at rest

Appendix C:

World Health Organization Functional Classification of Patients With PH	
Class 1	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class 2	Patients with PH 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 3	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope
Class 4	Patients with PH with inability to carry out any physical activity without symptoms. These patients' manifest signs of right-sided heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity

UPDATES:

Date:	Revision
4/23/2024	Revised
12/06/2023	Revised
6/8/2023	Revised
05/11/2023	P&T Committee Approval
4/27/2023	Revised
4/1/2023	Revised
10/5/2022	Revised
6/24/2022	Revised
5/5/2022	P&T Committee Approval
4/26/2022	Revised
3/21/2022	Revised
09/01/2021	Revised
7/27/2021	Revised
5/6/2021	Reviewed & P&T Committee Approval
4/19/2021	Revised
9/16/2020	Reviewed & P&T Committee Approval
08/25/2020	Revised
07/08/2020	Revised
4/14/2020	Revised
2/19/2020	Revised
11/19/2019	Reviewed
3/26/2019	Revised
10/1/2018	Revised
4/19/18	Revised
9/26/17	Revised
4/20/17	Reviewed
1/2016,	Revised
8/2014	Revised
6/2014	Revised
12/2013	Revised
8/2013	Revised
7/2013	Revised
2/2011	Revised
6/2005	Created

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