## Pulmonary Arterial Hypertension

### BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

### DESCRIPTION

The intent of the Pulmonary Arterial Hypertension (PAH) drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies.

**FDA-Approved Indications**

**Adcirca (tadalafil)**

Adcirca is an oral phosphodiesterase type 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

**Adempas (riociguat)**

Adempas is an oral soluble guanylate cyclase stimulator indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).

Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class.

**Flolan/Veletri (epoprostenol)**

Epoprostenol/Flolan/Veletri are intravenous prostanoids indicated for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

**Letairis (ambrisentan)**

Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1):

1. To improve exercise ability and delay clinical worsening
2. In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.
Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

**Opsumit (macitentan)**
Opsumit is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

**Orenitram (treprostinil)**
Orenitram is an oral prostanoid indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity. The study that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%).

When used as the sole vasodilator, the effect of Orenitram on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

**Remodulin (treprostinil)**
Remodulin is an intravenous prostanoid indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to diminish symptoms associated with exercise. Studies establishing effectiveness included patients with NYHA Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (19%).

In patients with PAH requiring transition from Flolan (epoprostenol sodium), Remodulin is indicated to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

**Revatio (sildenafil)**
Revatio (sildenafil) is an oral phosphodiesterase type 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II–III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%).

Compendial Use (not FDA-Approved use): Secondary Raynaud’s phenomenon *(Tablets only)*

**Tracleer (bosentan)**
Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with NYHA Functional Class II-IV symptoms and etiologies
of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). Tracleer is also indicated in pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.

**Tyvaso (treprostinil)**
Tyvaso is an inhaled prostanoid indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).

**Uptravi (selexipag)**
Uptravi is an oral prostacyclin receptor indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%).

**Ventavis (iloprost)**
Ventavis is an inhaled prostanoid indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

**POLICY**

Criteria for Initial Approval

I. **Adempas (riociguat)**
   A. **Pulmonary Arterial Hypertension**
      Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:
      1. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (Refer to Appendix)
      2. PAH was confirmed by right heart catheterization with all of the following pretreatment results:
         a. mPAP ≥ 25 mmHg
         b. PCWP ≤ 15 mmHg
         c. PVR > 3 Wood units

   B. **Chronic Thromboembolic Pulmonary Hypertension**
      Authorization of 24 months may be granted for treatment of CTEPH when ALL of the following criteria are met:
      1. Member has CTEPH defined as WHO Group 4 class of pulmonary hypertension (Refer to Appendix)
      2. Member meets either criterion (a) or criterion (b) below:
         a. Recurrent or persistent CTEPH after PEA
         b. Inoperable CTEPH with diagnosis confirmed by BOTH of the following (i. and ii.):
            i. Computed tomography (CT)/magnetic resonance imaging (MRI) angiography or pulmonary angiography
            ii. Pretreatment right heart catheterization with all of the following results:
• mPAP ≥ 25 mmHg
• PCWP ≤ 15 mmHg
• PVR > 3 Wood units

II. Adcirca (tadalafil)
Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:
1. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).
2. PAH was confirmed by either criterion (1) or criterion (2) below:
   a) Pretreatment right heart catheterization with all of the following results:
      i. mPAP ≥ 25 mmHg
      ii. PCWP ≤ 15 mmHg
      iii. PVR > 3 Wood units
   b) For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      i. Post cardiac surgery
      ii. Chronic heart disease
      iii. Chronic lung disease associated with prematurity
      iv. Congenital diaphragmatic hernia

III. Revatio (sildenafil)
A. Pulmonary Arterial Hypertension
Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:
1. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).
2. PAH was confirmed by either criterion (1) or criterion (2) below:
   a) Pretreatment right heart catheterization with all of the following results:
      i. mPAP ≥ 25 mmHg
      ii. PCWP ≤ 15 mmHg
      iii. PVR > 3 Wood units
   b) For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      i. Post cardiac surgery
      ii. Chronic heart disease
      iii. Chronic lung disease associated with prematurity
      iv. Congenital diaphragmatic hernia

B. Secondary Raynaud’s Phenomenon
Authorization or 24 months may be granted for treatment of secondary Raynaud’s phenomenon when the patient has had an inadequate response to one of the following medications:
1. Calcium channel blockers
2. Angiotensin receptor blockers
3. Selective serotonin reuptake inhibitors
4. Alpha blockers
5. Topical nitrates

IV. Epoprostenol, Flolan, Veletri (epoprostenol), and Ventavis (iloprost)
Indefinite authorization may be granted for treatment of PAH when ALL of the following criteria are met:

A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).

B. PAH was confirmed by either criterion (1) or criterion (2) below:
   1. Pretreatment right heart catheterization with all of the following results:
      a) mPAP ≥ 25 mmHg
      b) PCWP ≤ 15 mmHg
      c) PVR > 3 Wood units
   2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      a) Post cardiac surgery
      b) Chronic heart disease
      c) Chronic lung disease associated with prematurity
      d) Congenital diaphragmatic hernia

V. **Letairis (ambrisentan)**

Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:

A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).

B. PAH was confirmed by either criterion (1) or criterion (2) below:
   1. Pretreatment right heart catheterization with all of the following results:
      a) mPAP ≥ 25 mmHg
      b) PCWP ≤ 15 mmHg
      c) PVR > 3 Wood units
   2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      a) Post cardiac surgery
      b) Chronic heart disease
      c) Chronic lung disease associated with prematurity
      d) Congenital diaphragmatic hernia

VI. **Opsumit (macitentan)**

Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:

A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).

B. PAH was confirmed by either criterion (1) or criterion (2) below:
   1. Pretreatment right heart catheterization with all of the following results:
      a) mPAP ≥ 25 mmHg
      b) PCWP ≤ 15 mmHg
      c) PVR > 3 Wood units
   2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      a) Post cardiac surgery
      b) Chronic heart disease
      c) Chronic lung disease associated with prematurity
      d) Congenital diaphragmatic hernia

VII. **Orenitram (treprostinil)**

Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:
A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).

B. PAH was confirmed by either criterion (1) or criterion (2) below:
   1. Pretreatment right heart catheterization with all of the following results:
      a) mPAP ≥ 25 mmHg
      b) PCWP ≤ 15 mmHg
      c) PVR > 3 Wood units
   2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      a) Post cardiac surgery
      b) Chronic heart disease
      c) Chronic lung disease associated with prematurity
      d) Congenital diaphragmatic hernia

VIII. Remodulin (treprostinil)
Indefinite authorization may be granted for treatment of PAH when ALL of the following criteria are met:
A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).
B. PAH was confirmed by either criterion (1) or criterion (2) below:
   1. Pretreatment right heart catheterization with all of the following results:
      a) mPAP ≥ 25 mmHg
      b) PCWP ≤ 15 mmHg
      c) PVR > 3 Wood units
   2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      a) Post cardiac surgery
      b) Chronic heart disease
      c) Chronic lung disease associated with prematurity
      d) Congenital diaphragmatic hernia

IX. Tracleer (bosentan)
Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:
A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).
B. PAH was confirmed by either criterion (1) or criterion (2) below:
   1. Pretreatment right heart catheterization with all of the following results:
      a) mPAP ≥ 25 mmHg
      b) PCWP ≤ 15 mmHg
      c) PVR > 3 Wood units
   2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
      a) Post cardiac surgery
      b) Chronic heart disease
      c) Chronic lung disease associated with prematurity
      d) Congenital diaphragmatic hernia

X. Tyvaso (treprostinil)
Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:
A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).
B. PAH was confirmed by either criterion (1) or criterion (2) below:

1. Pretreatment right heart catheterization with all of the following results:
   a) mPAP ≥ 25 mmHg
   b) PCWP ≤ 15 mmHg
   c) PVR > 3 Wood units

2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
   a) Post cardiac surgery
   b) Chronic heart disease
   c) Chronic lung disease associated with prematurity
   d) Congenital diaphragmatic hernia

XI. Uptravi (selexipag)

Authorization of 24 months may be granted for treatment of PAH when ALL of the following criteria are met:

A. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (refer to Appendix).

B. PAH was confirmed by either criterion (1) or criterion (2) below:

1. Pretreatment right heart catheterization with all of the following results:
   a) mPAP ≥ 25 mmHg
   b) PCWP ≤ 15 mmHg
   c) PVR > 3 Wood units

2. For infants less than one year of age with any of the following conditions, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed:
   a) Post cardiac surgery
   b) Chronic heart disease
   c) Chronic lung disease associated with prematurity
   d) Congenital diaphragmatic hernia

Continuation of Therapy

Authorization of 24 months may be granted for members with PAH (and Raynaud’s phenomenon for Revatio or CTEPH for Adempas) who are currently receiving requested therapy through a paid pharmacy or medical benefit. Indefinite authorization will be given to Remodulin, Epoprostenol, Flolan, Veletri (epoprostenol), and Ventavis (iloprost).

The aforementioned drugs are considered not medically necessary for patients who do not meet the criteria set forth above.

Quantity Limits Apply

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

- Adcirca: 60 tablets per 30 days
- Adempas: 90 tablets per 30 days
- Epoprostenol/Flolan/Veletri: Not applicable
- Letairis: 30 tablets per 30 days
- Opsumit: 30 tablets per 30 days
- Orenitram: Not applicable
- Remodulin: Not applicable
- Revatio (and generic sildenafil): 360 tablets per 30 days, 720 mL per 30 days

A. For members who are < 18 years of age:

- Maximum 30 mg per day
- Authorization may be granted for tablets or suspension
B. For members who are ≥ 18 years of age:
   • For initial therapy: maximum 60 mg per day
   • For continuation of therapy: maximum 240 mg per day for members who have been titrated
     without adverse effects and experience clinical benefit with higher dose
C. Authorization may be granted for tablets only
   • Tracleer: 60 tablets per 30 days
     A. For members who weigh < 40 kg: maximum 125 mg per day
     B. For members who weigh ≥ 40 kg: maximum 250 mg per day
   • Tyvaso: 1 ampule per day
   • Uptravi: 60 tablets per 30 days
   • Ventavis: 9 ampules per day

APPENDIX

WHO Classification of Pulmonary Hypertension
WHO Group 1. Pulmonary Arterial Hypertension (PAH)
1.1 Idiopathic (IPAH)
1.2 Heritable PAH
   1.2.1 Germline mutations in the bone morphogenetic protein receptor type 2 (BMPR2)
   1.2.2 Activin receptor-like kinase type 1 (ALK1), endoglin (with or without hereditary hemorrhagic
telangiectasia), Smad 9, caveolin-1 (CAV1), potassium channel super family K member-3
     (KCNK3)
   1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4. Associated with:
   1.4.1 Connective tissue diseases
   1.4.2 HIV infection
   1.4.3 Portal hypertension
   1.4.4 Congenital heart diseases
   1.4.5 Schistosomiasis
1’. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
1”. Persistent pulmonary hypertension of the newborn (PPHN)

WHO Group 2. Pulmonary Hypertension Owing to Left Heart Disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies

WHO Group 3. Pulmonary Hypertension Owing to Lung Disease and/or Hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities

WHO Group 4. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

WHO Group 5. Pulmonary Hypertension with Unclear Multifactorial Mechanisms
5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis, segmental PH

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD-CM diagnostic codes.

- J1325 Injection, epoprostenol, 0.5 mg
- J3285 Injection, treprostinil, 1 mg
- J7686 Treprostinil, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, 1.74 mg
- Q4074 Iloprost, inhalation solution, FDA-approved final product, non-compounded, administered through DME, unit dose form, up to 20 micrograms

REFERENCES


POLICY HISTORY

Policy #: 05.01.89
Policy Creation: November 2015
Reviewed: April 2018
Revised: October 2018
Current Effective Date: October 19, 2018