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Pulmonary Arterial Hypertension

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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 (Alyq, 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%).

Compendial use: Secondary Raynaud's phenomenon

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%).

Limitation of use: Adding sildenafil to bosentan therapy does not result in any beneficial effect of exercise capacity.

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 12 months may be granted for treatment of PAH when ALL of the following criteria are/is met:

1. Member has PAH defined as WHO Group 1 class of pulmonary hypertension (Refer to Appendix A)
2. PAH was confirmed by right heart catheterization with all of the following pretreatment results:
 - a. mPAP \geq 25 mmHg
 - b. PCWP \leq 15 mmHg

- c. PVR > 3 Wood units

B. Chronic Thromboembolic Pulmonary Hypertension

Authorization of 12 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 A)
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 \geq 25 mmHg
 - PCWP \leq 15 mmHg
 - PVR > 3 Wood units

II. Adcirca (tadalafil)

A. Pulmonary Arterial Hypertension

Authorization of 12 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 (a) or criterion (b) below:
 - a) Pretreatment right heart catheterization with all of the following results:
 - i. mPAP > 20 mmHg
 - ii. PCWP \leq 15 mmHg
 - iii. PVR \geq 3 Wood units
 - b) For infants less than one year of age, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed.

B. Secondary Raynaud's Phenomenon

Authorization of 12 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

III. Revatio (sildenafil)

A. Pulmonary Arterial Hypertension

Authorization of 12 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 (a) or criterion (b) below:
 - a) Pretreatment right heart catheterization with all of the following results:
 - i. mPAP > 20 mmHg
 - ii. PCWP \leq 15 mmHg
 - iii. PVR \geq 3 Wood units
 - b) For infants less than one year of age, PAH was confirmed by Doppler echocardiogram if right heart catheterization cannot be performed.

B. Secondary Raynaud's Phenomenon

Authorization of 12 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 , and Veletri (epoprostenol)

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 A).
- 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 \geq 25 mmHg
 - b) PCWP \leq 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. Ventavis (epoprostenol)

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

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 \geq 25 mmHg
 - b) PCWP \leq 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. Letairis (ambrisentan)

Authorization of 12 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 A).
- 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 \geq 25 mmHg
 - b) PCWP \leq 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. Opsumit (macitentan)

Authorization of 12 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 A).
- 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 \geq 25 mmHg
 - b) PCWP \leq 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. Orenitram (treprostinil)

Authorization of 12 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 A).
- 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 \geq 25 mmHg
 - b) PCWP \leq 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. 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 A).
- 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 \geq 25 mmHg
 - b) PCWP \leq 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. Tracleer (bosentan)

A. Pulmonary Arterial Hypertension

Authorization of 12 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 A).
2. PAH was confirmed by either criterion (1) or criterion (2) below:
 - c) Pretreatment right heart catheterization with all of the following results:
 - iv. mPAP \geq 25 mmHg
 - v. PCWP \leq 15 mmHg
 - vi. PVR $>$ 3 Wood units
 - d) 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. Eisenmenger's Syndrome

Authorization of 12 months may be granted for treatment of members with WHO functional class III Eisenmenger's syndrome (refer to Appendix B).

XI. Tyvaso (treprostinil)

Authorization of 12 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 A).
- 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 \geq 25 mmHg
 - b) PCWP \leq 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

XII. Uptravi (selexipag)

Authorization of 12 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 A).
- 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 \geq 25 mmHg

- b) PCWP \leq 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 12 months may be granted for members with PAH (and Raynaud's phenomenon for Revatio or Adcirca or CTEPH for Adempas) who are currently receiving requested therapy through a paid pharmacy or medical benefit and who are experiencing benefit from therapy as evidenced by disease stability or disease improvement. Indefinite authorization will be given to Remodulin, Epoprostenol, Flolan, Veletri (epoprostenol), and Ventavis (iloprost) who are currently receiving requested therapy through a paid pharmacy or medical benefit and who are experiencing benefit from therapy as evidenced by disease stability or disease improvement.

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 \geq 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 \geq 40 kg: maximum 250 mg per day
- Tracleer soluble tablets: 120 tablets per 30 days
- Tyvaso: 1 ampule per day
- Uptravi: 60 tablets per 30 days
- Ventavis: 9 ampules per day

APPENDIX

Appendix

WHO Classification of Pulmonary Hypertension

WHO Group 1. Pulmonary Arterial Hypertension (PAH)

- 1.1 Idiopathic (IPAH)
- 1.2 Heritable PAH
- 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
- 1.5 PAH long-term responders to calcium channel blockers
- 1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
- 1.7 Persistent PH of the newborn syndrome

WHO Group 2. Pulmonary Hypertension Owing to Left Heart Disease

- 2.1 PH due to heart failure with preserved LVEF
- 2.2 PH due to heart failure with reduced LVEF
- 2.3 Valvular disease
- 2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

WHO Group 3. Pulmonary Hypertension Owing to Lung Disease and/or Hypoxia

- 3.1 Obstructive lung disease
- 3.2 Restrictive lung disease
- 3.3 Other lung disease with mixed restrictive and obstructive pattern
- 3.4 Hypoxia without lung disease
- 3.5 Developmental lung disorders

WHO Group 4. Pulmonary Hypertension Owing to pulmonary artery obstruction

- 4.1 Chronic thromboembolic PH
- 4.2 Other pulmonary artery obstructions
 - 4.2.1 Sarcoma (high or intermediate grade) or angiosarcoma
 - 4.2.2 Other malignant tumors
 - Renal carcinoma
 - Uterine carcinoma
 - Germ cell tumours of the testis
 - Other tumours
 - 4.2.3 Non-malignant tumours
 - Uterine leiomyoma
 - 4.2.4 Arteritis without connective tissue disease
 - 4.2.5 Congenital pulmonary artery stenosis
 - 4.2.6 Parasites
 - Hydatidosis

WHO Group 5. Pulmonary Hypertension with Unclear and/or Multifactorial Mechanisms

- 5.1 Hematologic disorders: Chronic hemolytic anemia, myeloproliferative disorders
- 5.2 Systemic and metabolic disorders: Pulmonary Langerhans cell histiocytosis, Gaucher disease, glycogen storage disease, neurofibromatosis, sarcoidosis
- 5.3 Others: chronic renal failure with or without hemodialysis, fibrosing mediastinitis
- 5.4 Complex congenital heart disease

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
- J3490 unclassified drugs(Revatio injection/Sildenafil injection)

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POLICY HISTORY

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