ORAL DRUGS FOR PULMONARY ARTERIAL HYPERTENSION (PAH)

BOSENTAN (Tracleer®), AMBRISENTAN (Letairis®), SILDENAFIL (Revatio®),
TADALAFIL (Adcirca®), RIOCIGUAT (Adempas®), MACITENTAN (Opsumit®),
TREPROSTINIL (Orenitram™), SELEXIPAG (Uptravi®)

UTILIZATION MANAGEMENT CRITERIA

| DRUG CLASS: | Oral Pulmonary Arterial Hypertension Agents |

<table>
<thead>
<tr>
<th>BRAND (generic) NAMES:</th>
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<tbody>
<tr>
<td>• Ambrisentan (Letairis): 5 mg and 10 mg strength tablets</td>
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<td>• Bosentan (Tracleer): 62.5 mg and 125 mg strength tablets</td>
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<td>• Macitentan (Opsumit): 10 mg strength tablet</td>
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<td>• Riociguat (Adempas): 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg strength tablets</td>
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<tr>
<td>• Selexipag (Uptravi): 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, and 1600 mcg strength tablets</td>
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<tr>
<td>• Sildenafil (Revatio): 20 mg strength tablet; 10 mg/mL (when reconstituted) oral suspension</td>
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<td>• Tadalafil (Adcirca): 20 mg strength tablet</td>
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<tr>
<td>• Treprostinil (Orenitram): 0.125 mg, 0.25 mg, 1 mg and 2.5 mg strength extended-release tablets</td>
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FDA-APPROVED INDICATIONS

Adcirca is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability.

Adempas is a soluble guanylate cyclase (sGC) stimulator 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.
- Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.
Letairis is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (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.

Opsumit is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) 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.

Orenitram is a prostacyclin vasodilator indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

Revatio is a phosphodiesterase-5 (PDE-5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) in adults to improve exercise ability and delay clinical worsening. **Limitation of Use:** Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

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.

Uptravi 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.

### COVERAGE AUTHORIZATION CRITERIA

The requested agent may be eligible for coverage when the following criteria are met:

1. For Adcirca, Letairis, Opsumit, Orenitram, Revatio, Tracleer, and Uptravi:
   - The requested medication is being used for treatment of pulmonary arterial hypertension (PAH/WHO Group 1).

2. For Adempas: The requested medication is being used for:
   - Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class; **OR**
   - Pulmonary Arterial Hypertension (PAH) (WHO Group 1) to improve exercise capacity, improve WHO functional class and to delay clinical worsening.
WHO Groups

Group 1- Pulmonary arterial hypertension (PAH)
- Idiopathic (IPAH)
- Heritable (HPAH)
  - Bone morphogenetic protein receptor type 2 (BMPR2)
  - Activin receptor-like kinase 1 gene (ALK1), endoglin (with or without haemorrhagic telangiectasia)
  - Unknown
- Drug- and toxin-induced
- Associated with (APAH):
  - Connective tissue diseases
  - Human immunodeficiency virus (HIV) infection
  - Portal hypertension
  - Congenital heart disease (CHD)
  - Schistosomiasis
  - Chronic haemolytic anaemia
- Persistent pulmonary hypertension of the newborn (PPHN)

Group 1'- Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)

Group 2- Pulmonary hypertension due to left heart diseases
- Systolic dysfunction
- Diastolic dysfunction
- Valvular disease

Group 3- Pulmonary hypertension due to lung diseases and/or hypoxemia
- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease (ILD)
- Other pulmonary diseases with mixed restrictive and obstructive pattern
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group 4- Chronic thromboembolic pulmonary hypertension (CTEPH)

Group 5- PH with unclear multifactorial mechanisms
- Haematological disorders: myeloproliferative disorders, splenectomy
- Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
- Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis
WHO Functional Class

The World Health Organization (WHO) has developed a system to help doctors determine how limited a patient is in their ability to do the activities of daily living. In general, patients with more severe PH tend to have a higher functional class.

- **Class I:** Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
- **Class II:** Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class III:** Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
- **Class IV:** Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

**DOSAGE AND ADMINISTRATION**

Adcirca: 40 mg once daily, with or without food. Dividing the dose (40 mg) over the course of the day is not recommended. Use with ritonavir requires dosage adjustments.

Adempas: Initiate treatment at 1 mg taken three times a day. For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg, three times a day. Increase dosage by 0.5 mg at intervals of no sooner than 2-weeks as tolerated to a maximum of 2.5 mg three times a day.

Letairis: Initiate treatment at 5 mg once daily. May be started with tadalafil. Titrate at 4-week intervals as needed and tolerated.

Opsumit: 10 mg once daily. Doses higher than 10 mg once daily have not been studied in patients with PAH and are not recommended.

Orenitram: Give with food. Swallow tablets whole; use only intact tablets. Starting dose: 0.25 mg BID or 0.125 mg TID. Titrate by 0.25 mg or 0.5 mg BID or 0.125 mg TID, not more than every 3 to 4 days as tolerated.

Revatio: Tablet and oral suspension: 5 mg or 20 mg three times a day, 4–6 hours apart.

Tracleer: Initiate at 62.5 mg twice daily with or without food for 4 weeks, and then increase to 125 mg twice daily. Patients with low body weight (12 years old: Initial and maintenance dose is 62.5 mg twice daily.

Uptravi: Starting dose is 200 mcg twice daily; increase dose to the highest tolerated dose up to 1600 mcg twice daily.

**See full prescribing information for complete dosage and administration**
REFERENCES:

Adcirca (tadalafil) [prescribing information]. Eli Lilly and Company. April 2015.

Adempas (riociguat) [prescribing information]. Bayer HealthCare Pharmaceuticals Inc. September 2014.

Letairis (ambrisentan) [prescribing information]. Gilead Sciences, Inc. October 2015.

Opsumit (macitentan) [prescribing information]. Actelion Pharmaceuticals US, Inc. December 2015.

Orenitram (treprostinil) [prescribing information]. United Therapeutics Corp. October 2014.

Revatio (sildenafil) [prescribing information]. Pfizer Inc. April 2015.

Tracleer (bosentan) [prescribing information]. Actelion Pharmaceuticals US, Inc. December 2015.

Uptravi (selexipag) [prescribing information]. Actelion Pharmaceuticals US, Inc. December 2015.

POLICY IMPLEMENTATION/UPDATE INFORMATION

December 2015: Policy revised to add new to market drug Uptravi.