Pharmacy Medical Necessity Guidelines: Pulmonary Hypertension Medications

Effective: January 8, 2019

Prior Authorization Required  √  Type of Review – Care Management
Not Covered  √  Type of Review – Clinical Review

Pharmacy (RX) or Medical (MED) Benefit  RX/ MED  Department to Review  RxUM/ PRECERT /MM

These pharmacy medical necessity guidelines apply to the following:

**Commercial Products**

- Tufts Health Plan Commercial products – large group plans
- Tufts Health Plan Commercial products – small group and individual plans
- Tufts Health Freedom Plan products – large group plans
- Tufts Health Freedom Plan products – small group plans

- CareLink℠ – Refer to CareLink Procedures, Services and Items Requiring Prior Authorization

**Tufts Health Public Plans Products**

- Tufts Health Direct – A Massachusetts Qualified Health Plan (QHP) (a commercial product)
- Tufts Health Together – MassHealth MCO Plan and Accountable Care Partnership Plans
- Tufts Health RITogether – A Rhode Island Medicaid Plan

Fax Numbers:

- Adcirca, Adempas, Letairis, Opsumit, Orenitram, Revatio, sildenafil, Tracleer, Uptravi
  RXUM: 617.673.0988
- Epoprostenol, Flolan, Remodulin, Tyvaso, Veletri, Ventavis
  All plans except Tufts Health Direct – Health Connector
  PRECERT: 617.972.9409
  Tufts Health Direct – Health Connector Only
  MM: 888.415.9055

Note: This guideline does not apply to Medicare Members (includes dual eligible Members).

**OVERVIEW**

**FOOD AND DRUG ADMINISTRATION-APPROVED INDICATIONS**

- **Adcirca** (tadalafil) is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with New York Heart Association (NYHA) Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

- **Adempas** (riociguat) is a soluble guanylate cyclase stimulator indicated:
  - For the treatment of adults with PAH, (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy was shown in patients on Adempas (riociguat) 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%).
  - 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** (epoprostenol sodium) is a prostacyclin vasodilator indicated for the treatment of PAH (WHO Group 1) 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) is an endothelin receptor antagonist (ERA) indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening and 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) is an ERA indicated for the treatment of 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 (macitentan) 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 (macitentan) 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) is a prostacyclin vasodilator indicated for the treatment of PAH (WHO Group I) 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 congenital systemic-to-pulmonary shunts (23%), or PAH associated with connective tissue diseases (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. Orenitram (treprostinil) is probably most useful to replace subcutaneous, intravenous, or inhaled treprostinil, but this use has not been studied.

Remodulin (treprostinil sodium) is a prostacyclin vasodilator indicated:
- For the treatment of PAH (WHO Group I) 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) to diminish the rate of clinical deterioration. The risks and benefits of each drug should be carefully considered prior to transition.

Revatio (sildenafil) is a PDE5 inhibitor indicated for the treatment of PAH (WHO Group I) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio (sildenafil) was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with NYHA Functional Class II–III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (CTD) (25%). Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

Tracleer (bosentan) is an ERA indicated for the treatment of PAH (WHO Group I)
- In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominately patients with WHO 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%).
- In pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance, which is expected to result in an improvement in exercise ability.

Tyvaso (treprostinil) is a prostacyclin vasodilator, available as an inhalation solution and indicated for the treatment of PAH (WHO Group I) 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%). The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase type 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration.

Uptravi (selexipag) is a prostacyclin receptor antagonist indicated for the treatment of 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%).

Veletri (epoprostenol sodium) is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group I) to improve exercise capacity. Studies establishing effectiveness included

Pharmacy Medical Necessity Guidelines: Pulmonary Hypertension Medications
predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Ventavis (iloprost) is a synthetic analog of prostacyclin indicated for the treatment of 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%).

**COVERAGE GUIDELINES**

**Pulmonary Arterial Hypertension (PAH)**

The plan may authorize coverage of Adcirca (tadalafil), Adempas (riociguat), generic epoprostenol sodium, Flolan/Veletri (epoprostenol sodium), Letairis (ambrisentan), Opsumit (macitentan), Orenitram (treprostinil), Remodulin (treprostinil sodium), Tracleer (bosentan) tablets/tablets for oral suspension, Tyvaso (treprostinil), Uptravi (selexipag), Ventavis (iloprost), or sildenafil tablets/oral suspension for Members when the following criteria are met:

*See “Additional Coverage Criteria for Flolan/Veletri for PAH” below.*

1. The Member must have a definitive diagnosis of PAH (World Health Organization [WHO] Group I; see below) from a cardiologist or pulmonologist and confirmed by right heart catheterization

   WHO Classification of Pulmonary Hypertension
   Group 1:
   a. Idiopathic PAH (primary pulmonary hypertension)
   b. Heritable PAH
   c. Drug- and toxin-induced PAH
   d. PAH associated with other diseases and conditions (APAH)
      - Connective tissue diseases
      - Human immunodeficiency virus infection
      - Portal hypertension
      - Congenital heart disease
      - Schistosomiasis
   e. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
   f. Persistent pulmonary hypertension of the newborn (PPHN)

   AND

2. The pulmonary hypertension has progressed despite surgical treatment and/or maximal medical treatment of the underlying condition

   AND

3. The medication used for treatment is consistent with its Food and Drug Administration (FDA) approved functional class (see corresponding chart below)

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved Functional Class of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adempas</td>
<td>WHO Class II and III (Pulmonary Arterial Hypertension)</td>
</tr>
<tr>
<td>epoprostenol</td>
<td>NYHA Class III and IV</td>
</tr>
<tr>
<td>(Flolan/Veletri)</td>
<td></td>
</tr>
<tr>
<td>Letairis</td>
<td>WHO Class II and III</td>
</tr>
<tr>
<td>Opsumit</td>
<td>WHO Class II and III</td>
</tr>
<tr>
<td>Orenitram</td>
<td>WHO Class II and III</td>
</tr>
<tr>
<td>Remodulin</td>
<td>NYHA Class II, III, and IV</td>
</tr>
<tr>
<td>sildenafil (Revatio)</td>
<td>NYHA Class II and III</td>
</tr>
<tr>
<td>tadalafil (Adcirca)</td>
<td>NYHA Class II and III</td>
</tr>
<tr>
<td>Tracleer</td>
<td>WHO Class II, III, and IV</td>
</tr>
<tr>
<td>Tyvaso</td>
<td>NYHA Class III</td>
</tr>
<tr>
<td>Uptravi</td>
<td>WHO Class II and III</td>
</tr>
<tr>
<td>Ventavis</td>
<td>NYHA Class III and IV</td>
</tr>
</tbody>
</table>

**Note:** Please refer to References Section for a description of NYHA and WHO Functional Class descriptions.
Additional Coverage Criteria for Flolan / Veletri (epoprostenol sodium) for PAH
The plan requires Members initiating treatment with epoprostenol sodium to utilize the generic version (provided they meet the pharmacy coverage guidelines described above) prior to authorization of brand name Flolan (epoprostenol sodium) or Veletri (epoprostenol sodium). Coverage of Flolan/Veletri (epoprostenol sodium) will be considered for Members who have failed an adequate trial of or are unable to tolerate generic epoprostenol.

Chronic-Thromboembolic Pulmonary Hypertension
The plan may authorize coverage of Adempas (riociguat) for Members when the following criteria are met:

1. The Member has a definitive diagnosis of PAH (WHO group 4) confirmed by right heart catheterization

2. The prescriber is a cardiologist or pulmonologist

3. Documentation of one of the following:
   a. The chronic thromboembolic pulmonary hypertension persists or recurs after surgical treatment
   b. Member is diagnosed as inoperable by a center specializing in chronic thromboembolic pulmonary hypertension or pulmonary thromboendarterectomy

LIMITATIONS
- The plan will not authorize coverage of generic epoprostenol sodium, Flolan/Veletri (epoprostenol sodium), Adempas (riociguat), Letairis (ambrisentan), Osimpt (macitentan), Orenitram (treprostinil), Remodulin (treprostinil sodium), Tracleer (bosentan), Tyvaso (treprostinil), Uptravi (selexipag), Ventavis (loprost), Adcirca (tadalafil) and sildenafil tablets/oral suspension for pulmonary hypertension secondary to the following conditions:
  o Diseases of the left atrium and ventricle such as congestive heart failure or cardiomyopathy
  o Diseases of the mitral and aortic valves
  o Chronic lung diseases such as chronic obstructive pulmonary disease, restrictive pulmonary disease or interstitial pulmonary disease
  o Obstructive sleep apnea or other sleep disorders involving breathing or alveolar hyperventilation disorders
- Adempas (riociguat) will not be approved if administered concomitantly with phosphodiesterase inhibitors or nitrates.

CODES
The following HCPCS/CPT code(s) are:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1325</td>
<td>Injection, epoprostenol, 0.5mg</td>
</tr>
<tr>
<td>J3285</td>
<td>Injection, treprostinil</td>
</tr>
<tr>
<td>J7686</td>
<td>Treprostinil, inhalation solution, FDA-approved final product, noncompounded, administered through DME, unit dose form, 1.74 mg</td>
</tr>
<tr>
<td>Q4074</td>
<td>Iloprost, inhalation solution, administered through DME, up to 20mcg</td>
</tr>
</tbody>
</table>

REFERENCES
New York Heart Association Pulmonary Arterial Hypertension Functional Classification of Symptoms

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation</td>
</tr>
<tr>
<td></td>
<td>Ordinary physical activity does not cause symptoms.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation</td>
</tr>
<tr>
<td></td>
<td>Comfortable at rest. Ordinary physical activity causes symptoms</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation</td>
</tr>
<tr>
<td></td>
<td>Comfortable at rest. Less than ordinary activity causes symptoms</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to carry on any physical activity</td>
</tr>
<tr>
<td></td>
<td>Symptoms present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>
World Health Organization Pulmonary Arterial Hypertension Functional Classification of Symptoms

<table>
<thead>
<tr>
<th>Class</th>
<th>Limitation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>No limitation</td>
<td>Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class II</td>
<td>Slight limitation</td>
<td>Comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class III</td>
<td>Marked limitation</td>
<td>Comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Inability to carry on any physical activity</td>
<td>Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>

REFERENCES

1. May 10, 2005: No changes.
2. September 13, 2005: Add Ventavis (iloprost) to the TOPIC, CLINICAL COVERAGE CRITERIA and LIMITATIONS. Change criteria #1 from "The Member must have the definitive diagnosis of either Primary or Secondary symptomatic Pulmonary Hypertension (PH) from a cardiologist or pulmonologist confirmed by the two diagnostic tests, Right-heart cardiac catheterization and Echocardiogram showing right atrial and ventricular enlargement" to "The Member must have a definitive diagnosis of pulmonary artery hypertension (WHO group I) from a cardiologist or pulmonologist and confirmed by right heart catheterization". Add criteria #3, "The Member’s symptoms are New York Heart Association (NYHA) class III to IV" (see table above).
3. November 8, 2005: Change the brand name "Viagra" in the Topic, Coverage Criteria and Coverage Limitations to sildenafil. Add the coverage limitations: "Tufts Health Plan may authorize coverage of Viagra for pulmonary hypertension when the dosage for sildenafil exceeds 20mg three times a day."
4. October 10, 2006: No changes.
7. September 8, 2009: For effective date December 1, 2009: Added guidelines for "*Coverage for Flolan" Added WHO class II to FDA approved functional class for Tracleer.
9. January 1, 2010: Removal of Tufts Health Plan Medicare Preferred language (separate criteria have been created specifically for Tufts Health Plan Medicare Preferred)
11. May 11, 2010: Clarified dosage form of sildenafil and Revatio as tablets
17. February 11, 2014: Added Adempas (riociguat) and Opsumit (macitentan) to Medical Necessity Guidelines.
18. June 10, 2014: Added Orenitram (treprostinil) to Medical Necessity Guidelines, and Updated WHO Group I classifications under criteria #1: Removed: Chronic hemolytic anemias and Added: Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis and Persistent pulmonary hypertension of the newborn (PPHN). Updated criterion #4 under Chronic-Thromboembolic Pulmonary Hypertension to "Member is diagnosed as inoperable by a center specializing in chronic thromboembolic pulmonary hypertension or pulmonary thromboendarterectomy."
19. December 9, 2014: Added sildenafil oral suspension to Medical Necessity Guidelines. Removed authorization of coverage of Viagra tablets when the dosage for sildenafil exceeds 20mg three times a day.
BACKGROUND, PRODUCT AND DISCLAIMER INFORMATION

Pharmacy Medical Necessity Guidelines have been developed for determining coverage for plan benefits and are published to provide a better understanding of the basis upon which coverage decisions are made. The plan makes coverage decisions on a case-by-case basis considering the individual member’s health care needs. Pharmacy Medical Necessity Guidelines are developed for selected therapeutic classes or drugs found to be safe, but proven to be effective in a limited, defined population of patients or clinical circumstances. They include concise clinical coverage criteria based on current literature review, consultation with practicing physicians in the service area who are medical experts in the particular field, FDA and other government agency policies, and standards adopted by national accreditation organizations. The plan revises and updates Pharmacy Medical Necessity Guidelines annually, or more frequently if new evidence becomes available that suggests needed revisions.

For self-insured plans, coverage may vary depending on the terms of the benefit document. If a discrepancy exists between a Pharmacy Medical Necessity Guideline and a self-insured Member’s benefit document, the provisions of the benefit document will govern.

Treating providers are solely responsible for the medical advice and treatment of members. The use of this policy is not a guarantee of payment or a final prediction of how specific claim(s) will be adjudicated. Claims payment is subject to member eligibility and benefits on the date of service, coordination of benefits, referral/authorization and utilization management guidelines when applicable, and adherence to plan policies and procedures and claims editing logic.