PULMONARY ARTERIAL HYPERTENSION AGENTS

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Length of Authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adcirca</td>
<td>tadalafl</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Adempas</td>
<td>riociguat</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Folan</td>
<td>epoprostenol sodium</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Letairis</td>
<td>ambrisentan</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Opremit</td>
<td>macitentan</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Orenitram</td>
<td>treprostinil, oral</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Remodulin</td>
<td>treprostinil, injection</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Revatio</td>
<td>sildenafil citrate</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Tracleer</td>
<td>bosentan</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Tyvaso</td>
<td>treprostinil, inhalation</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Upptraj</td>
<td>selexipag</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Veletri</td>
<td>epoprostenol sodium</td>
<td>Calendar Year</td>
</tr>
<tr>
<td>Ventavis</td>
<td>iloprost</td>
<td>Calendar Year</td>
</tr>
</tbody>
</table>

Approvable Criteria:

I. **For ALL Agents**
   
   A. Adult patient only. *Safety and efficacy has not been proven in the pediatric population. However, there is limited published data regarding the use of sildenafil in pediatric patients.*
   
   B. Practitioner specializes in Pulmonology or Cardiology.

III. **Adcirca (oral)**
   
   A. For the treatment of PAH as classified by WHO group 1 to improve exercise ability.
   
   B. Member is not currently using any form of nitrate therapy.
   
   C. Member has a trial and failure or contraindicated to Calcium Channel Antagonists (long-acting nifedipine, diltiazem, or amlodipine).

XII. **Adempas (oral)**

   A. For the treatment of PAH as classified by WHO group 1 in members with NYHA class II to III symptoms to improve exercise ability and decrease the rate of clinical worsening.
   
   B. Member is not taking concurrent therapy with any nitrates, nitric oxide donors, or PDE-5 inhibitors (i.e., sildenafil, tadalafl, Levitra, dipyridamole, or theophylline).
   
   C. Member has tried and failed or intolerant to Revatio or Adcirca.
   
   D. QL = 90 x 30 DAYS

   OR

Continued on the following page...
PULMONARY ARTERIAL HYPERTENSION AGENTS
A. For the treatment of persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) WHO Group 4.
B. Member has had prior surgical treatment or CTEPH is inoperable.
C. Member is not taking concurrent therapy with any nitrates, nitric oxide donors, or PDE-5 inhibitors (i.e., sildenafil, tadalafil, Levitra, dipyridamole, or theophylline).
D. QL = 90 x 30 DAYS

X. Flolan (infused)
A. For the long-term intravenous treatment of primary pulmonary hypertension and pulmonary hypertension associated with the scleroderma spectrum of disease in NYHA class III and class IV members who do not respond adequately to conventional therapy.
B. Member has tried and failed or intolerant to Revatio or Adcirca or is categorized as functional class IV, where Revatio or Adcirca is not indicated.

IV. Letairis (oral)
A. For the treatment of PAH as classified by WHO group 1 in members with NYHA class II or III symptoms to improve exercise capacity and delay clinical worsening.
B. Member has tried and failed or intolerant to Revatio or Adcirca.
C. QL = 30 x 30 DAYS

VI. Opsumit (oral)
A. For the treatment of PAH as classified by WHO group 1 in members with NYHA functional class II or III symptoms to delay disease progression.
B. Member has tried and failed or intolerant to Revatio or Adcirca AND Letairis.
C. QL = 30 x 30 DAYS

XIII. Orenitram (oral)
A. For the treatment of PAH as classified by WHO group 1 in members with NYHA class II to III symptoms to improve exercise ability and decrease the rate of clinical worsening.
B. Member has tried two oral therapies for PAH (or is currently receiving them) from two of the three following categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor (e.g., Revatio, Adcirca, sildenafil), one endothelin receptor antagonist (ERA) [e.g., Tracleer, Letairis or Opsumit], or Adempas OR member is receiving or has received in the past one prostacyclin therapy (e.g., Remodulin, Tyvaso, Ventavis, or epoprostenol injection [Flolan, Veltari, generics]) or a prostacyclin receptor agonist (i.e., Uptravi) for PAH.

Continued on the following page...
PULMONARY ARTERIAL HYPERTENSION AGENTS

IX. Remodulin *(infused)*
   A. For the treatment of PAH (WHO group 1) in members with NYHA class II to IV symptoms to diminish symptoms associated with exercise.
   B. Continuous intravenous (IV) infusion should be reserved for those who are intolerant of the subcutaneous (SQ) route.
   C. Member has tried and failed or intolerant to Revatio or Adcirca or is categorized as functional class IV, where Revatio or Adcirca is not indicated.

II. Revatio *(oral)*
   A. For the treatment of PAH (Pulmonary Arterial Hypertension) as classified by World Health Organization (WHO) group 1 to improve exercise ability and delay clinical worsening.
   B. Member is not currently using any form of nitrate therapy.
   C. Member has a trial and failure or contraindicated to Calcium Channel Antagonists (long-acting nifedipine, diltiazem, or amlodipine).

V. Tracleer *(oral)* *(Letairis is Preferred Endothelin Receptor Antagonist)*
   A. For the treatment of PAH as classified by WHO group 1 in members with NYHA class II to IV symptoms to improve exercise ability and decrease the rate of clinical worsening.
   B. Member has tried and failed or intolerant to Revatio or Adcirca AND Letairis or is categorized as functional class IV, where Revatio or Adcirca is not indicated.
   C. QL = 60 x 30 DAYS

VII. Tyvaso *(inhaled)*
   A. To increase walk distance in members with WHO group 1 PAH and New York Heart Association (NYHA) class III symptoms.
   B. Member has tried and failed or intolerant to Revatio or Adcirca.
   C. QL = 30 x 30 DAYS

XIV. Uptravi *(oral)*
   A. For the treatment of PAH as classified by WHO group 1 in members with NYHA class II to III symptoms to delay disease progression and reduce the risk of hospitalization for PAH.
   B. Member has tried two oral therapies for PAH (or is currently receiving them) from two of the three following categories (either alone or in combination) each for ≥ 60 days: one phosphodiesterase type 5 (PDE5) inhibitor (e.g., Revatio, Adcirca, sildenafil), one endothelin receptor antagonist (ERA) [e.g., Tracleer, Letairis or Opsumit], or Adempas OR member is receiving or has received in the past one prostacyclin therapy (e.g., Orenitram, Remodulin, Tyvaso, Ventavis, or epoprostenol injection [Flolan, Velteli, generics]).
   C. QL = 60 x 30 DAYS

Continued on the following page...
PULMONARY ARTERIAL HYPERTENSION AGENTS

XI. Veletri (infused)
   A. For the long-term intravenous treatment of adult members with NYHA class III or IV primary pulmonary hypertension or adults with pulmonary hypertension due to scleroderma (systemic sclerosis).
   B. Member has tried and failed or intolerant to Revatio or Adcirca or is categorized as functional class IV, where Revatio or Adcirca is not indicated.

VIII. Ventavis (inhaled)
   A. For the treatment of PAH as classified by WHO group 1 in members with NYHA class III or IV symptoms.
   B. Member has tried and failed or intolerant to Revatio or Adcirca or is categorized as functional class IV, where Revatio or Adcirca is not indicated.
   C. QL = 270 x 30 DAYS

Approve for Calendar Year
*May be renewed if improvement in exercise capacity, functional class, and/or a delay in clinical worsening is demonstrated.

SPECIALTY PHARMACY PRODUCT

Non-approvable diagnosis:
- Sexual dysfunction
- Benign Prostatic Hypertrophy (BPH)
- Raynaud phenomenon
- Achalasia/Esophageal motility disorders

The NYHA Classification System

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I (Mild)</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).</td>
</tr>
<tr>
<td>Class II (Mild)</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class III (Moderate)</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.</td>
</tr>
<tr>
<td>Class IV (Severe)</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>

Continued on the following page...
PULMONARY ARTERIAL HYPERTENSION AGENTS

Treatment Options based on Functional Class:

- **Functional Class I-II**
  - **Calcium channel antagonists** (Long-acting nifedipine, diltiazem or amlodipine)
    - IPAH patients who demonstrate vasoreactivity may benefit from CCB therapy. A positive acute vasodilator response is defined as a fall in mPAP ≥ 10mm Hg to ≤ 40mm Hg, with an unchanged or increased cardiac output, when challenged with inhaled nitric oxide, IV adenosine or IV epoprostenol during right heart cardiac catheterization.
    - Vasoreactivity is uncommon (10-15% of patients tested), and long-term clinical response can be expected in about half of those patients
  - **For patients who are not a candidate for, or have failed CCB**
    - Phosphodiesterase inhibitors (sildenafil, tadalafil)
    - Endothelin Antagonists (bosentan, ambrisentan),
    - Prostanoids (treprostinil)

- **Functional Class III**
  - Phosphodiesterase inhibitors (sildenafil, tadalafil), for early Class III disease, or
  - Endothelin Antagonists (bosentan, ambrisentan), for early Class III disease, or
  - Prostanoids (epoprostenol, treprostinil, iloprost) for more advanced Class III disease

- **Functional Class IV**
  - Prostanoids (epoprostenol- preferred, treprostinil, iloprost)*

References:

- Adcirca prescribing information. Indianapolis, IN: Eli Lilly Co; April 2015.
- Letairis prescribing information. Foster City, CA: Gilead; October 2015.