Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

Effective Date: 06/11/2020

Treatment Guidelines for Pulmonary Arterial Hypertension

Flolan® (epoprostenol)
Remodulin® (treprostinil)
Tyvaso® (treprostinil)
Veletri® (epoprostenol)
Ventavis® (iloprost)

FDA approval: Various
HCPCS: Flolan/Veletri - J1325; Remodulin - J3285; Tyvaso - J7686; Ventavis - Q4074
Benefit: Both

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Diagnosis of World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) confirmed by right heart catherization and not ECHO alone, pulmonary arterial pressure (PAPm) > 25 mmHg
   b. Patient is ≥ 18 years of age
   c. Trial and failure, intolerance, or a contraindication to the preferred products as listed in the BCBSM/BCN utilization management drug list and/or BCBSM/BCN prior authorization and step therapy documents

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limit: Quantity limits are as follows (based on how supplied; refer to background information):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>epoprostenol (generic)</td>
<td>Highly variable; 20 to 40 ng/kg/min for continuous IV infusion; titrate every 15 minutes</td>
</tr>
<tr>
<td>epoprostenol (Flolan, Veletri)</td>
<td>Same as generic epoprostenol</td>
</tr>
<tr>
<td>iloprost (Ventavis)</td>
<td>2.5 to 5 mcg nebulized 6 to 9 times per day</td>
</tr>
<tr>
<td>treprostinil (Remodulin)</td>
<td>Highly variable; 20 to 40 ng/kg/min for continuous SQ or IV infusion; titrate weekly</td>
</tr>
<tr>
<td>treprostinil (Tyvaso)</td>
<td>54 mcg nebulized four times per day</td>
</tr>
</tbody>
</table>

   b. Authorization may be reviewed at least annually to confirm that the medication is effective.
Therapeutic considerations:

A. FDA approved indication / Diagnosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flolan (epoprostenol)</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (WHO group 1) to improve exercise capacity</td>
</tr>
<tr>
<td>Veletri (epoprostenol)</td>
<td></td>
</tr>
<tr>
<td>Remodulin (treprostinil)</td>
<td>Treatment of pulmonary arterial hypertension (PAH) (WHO group 1) to diminish symptoms associated with exercise; to diminish the rate of clinical deterioration in patients with PAH requiring transition from epoprostenol</td>
</tr>
<tr>
<td>Tyvaso (treprostinil)</td>
<td></td>
</tr>
<tr>
<td>Ventavis (iloprost)</td>
<td>For the treatment of pulmonary arterial hypertension (PAH) (WHO group 1) in patients with New York Heart Association (NYHA) class III or IV symptoms to improve exercise tolerance, symptoms, and diminish clinical deterioration</td>
</tr>
</tbody>
</table>

*Please refer to most recent prescribing information.

B. Background Information

a. The World Health Organization (WHO) classifies pulmonary hypertension (PH) in five groups, based on underlying etiology of PH
b. Patients diagnosed with Group 1 pulmonary arterial hypertension (PAH) have generally irreversible disease and may require treatment with PAH-specific therapies
c. For patients with Groups 2-5, PH may be reversible and therapy should be directed at treating the underlying cause
d. Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin and prostacyclin analogs (epoprostenol, treprostinil, and iloprost), endothelin-receptor antagonists (ETAs) (ambrisentan, bosentan, macitentan), PDE-5 inhibitors (sildenafil, tadalafil), and soluble guanylate cyclase stimulators (riociguat)
e. The place in therapy of individual agents for PAH is not well defined and is typically symptom driven
f. Generally, a step-wise approach is used to manage patients
g. In early disease or with less severe symptoms, oral therapies may be used
h. As symptoms progress, inhaled or injectable therapies, such as epoprostenol, iloprost and treprostinil, become necessary
i. Two US-based treatment guidelines for PAH are currently available—the American College of Chest Physicians (ACCP) updated in 2007 and American College of Cardiology Foundation (ACCF) updated in 2009
j. The ACCF guidelines are consensus-based, while ACCP’s are evidence-based
k. The ACCP recommendations for choice of treatment are based on functional class
l. The recommended therapies have been evaluated mainly in those with IPAH (idiopathic PAH) or PAH associated with connective tissue disease or anorexigen use, thus, extrapolations to other forms of PAH should be made with caution

C. Efficacy

*Please refer to most recent prescribing information.
D. **Medication Safety Considerations**

Black Box Warning: No

*Please refer to most recent prescribing information.*

E. **Dosing and administration**

*Please refer to most recent prescribing information.*

F. **How supplied**

   a. epoprostenol (generic, Flolan, Veletri): 0.5 mg, 1.5 mg intravenous powder for solution
   b. iloprost (Ventavis): 10 mcg/ml, 20 mcg/ml inhalation solution
   c. treprostinil (Remodulin): 1 mg/ml, 2.5 mg/ml, 5 mg/ml, 10 mg/ml injection solution
   d. treprostinil (Tyvaso): 0.6 mg/ml inhalation solution

References:

14. Marion, DW. Pulmonary hypertension. In: UpToDate, Basow, DS (Ed), UptoDate, Waltham, MA, 2013.


### Policy History

<table>
<thead>
<tr>
<th>#</th>
<th>Date</th>
<th>Change Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.7</td>
<td>Effective Date: 06/11/2020</td>
<td>Annual Review of Medical Policy</td>
</tr>
<tr>
<td>1.6</td>
<td>Effective Date: 06/06/2019</td>
<td>Added trial and failure of preferred products statement</td>
</tr>
<tr>
<td>1.5</td>
<td>Effective Date: 02/14/2019</td>
<td>Annual Review of Medical Policy</td>
</tr>
<tr>
<td>1.4</td>
<td>Effective Date: 07/05/2017</td>
<td>PA added to MAPPO and BCNA for Flolan, Remodulin, Tyvaso, Veletri, and Ventavis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Line of Business</th>
<th>PA Required (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCBS</td>
<td>No</td>
</tr>
<tr>
<td>BCN</td>
<td>No</td>
</tr>
<tr>
<td>MAPPO</td>
<td>Yes</td>
</tr>
<tr>
<td>BCNA</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1.3</th>
<th>Effective Date: 08/14/2014</th>
<th>Add QL to Orenitram and updated information on dosing, safety, pregnancy &amp; lactation, adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>Effective Date: 05/08/2014</td>
<td>Criteria Update: Updated to include Orenitram</td>
</tr>
<tr>
<td>1.1</td>
<td>Effective Date: 02/06/2014</td>
<td>Criteria Update</td>
</tr>
<tr>
<td>1.0</td>
<td>Effective Date: 02/07/2013</td>
<td>Criteria Update</td>
</tr>
</tbody>
</table>

* The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or [http://dailymed.nlm.nih.gov/dailymed/index.cfm](http://dailymed.nlm.nih.gov/dailymed/index.cfm).