Clinical Policy: Epoprostenol (Flolan, Veletri)
Reference Number: CP.PHAR.192
Effective Date: 03.16
Last Review Date: 02.21
Line of Business: Commercial, HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Epoprostenol (Flolan®, Veletri®) is a prostacyclin.

FDA Approved Indication(s)
Flolan and Veletri are indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) to improve exercise capacity.

Studies establishing effectiveness included predominantly patients with New York Heart Association (NYHA) Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Flolan and Veletri are necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Pulmonary Arterial Hypertension (must meet all):
      1. Diagnosis of PAH;
      2. Prescribed by or in consultation with a cardiologist or pulmonologist;
      3. Failure of a calcium channel blocker (see Appendix B), unless member meets one of the following (a or b):
         a. Inadequate response or contraindication to acute vasodilator testing;
         b. Contraindication or clinically significant adverse effects to calcium channel blockers are experienced;
      4. If request is for brand Flolan or brand Veletri, medical justification supports inability to use generic epoprostenol sodium (e.g., contraindication to excipients);
      5. Provider must submit treatment plan detailing pump rate, dose and quantity (in mL).

   Approval duration:
   Medicaid/HIM – 6 months
   Commercial – Length of Benefit

   B. Other diagnoses/indications
      1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is
II. Continued Therapy  
A. Pulmonary Arterial Hypertension (must meet all):  
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;  
2. Member is responding positively to therapy;  
3. Provider must submit treatment plan detailing pump rate, dose and quantity (in mL).  
   Approval duration:  
   Medicaid/HIM – 12 months  
   Commercial – Length of Benefit  

B. Other diagnoses/indications (must meet 1 or 2):  
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.  
   Approval duration: Duration of request or 6 months (whichever is less); or  
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:  
A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information  
Appendix A: Abbreviation/Acronym Key  
FC: functional class  
FDA: Food and Drug Administration  
NYHA: New York Heart Association  
PAH: pulmonary arterial hypertension  
PH: pulmonary hypertension  
WHO: World Health Organization

Appendix B: Therapeutic Alternatives  
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>nifedipine (Adalat® CC, Afeditab® CR, Procardia®, Procardia XL®)</td>
<td>60 mg PO QD; may increase to 120 to 240 mg/day</td>
<td>240 mg/day</td>
</tr>
<tr>
<td>diltiazem (Dilacor XR®, Dilt-XR®, Cardizem® CD, Cartia XT®, Tiazac®, Taztia XT®, Cardizem® LA, Matzim® LA)</td>
<td>720 to 960 mg PO QD</td>
<td>960 mg/day</td>
</tr>
</tbody>
</table>
### Appendix C: Contraindications/Boxed Warnings

- **Contraindication(s):**
  - Congestive heart failure due to severe left ventricular systolic dysfunction
  - Pulmonary edema
  - Hypersensitivity to the drug or to structurally related compounds
- **Boxed warning(s):** none reported

### Appendix D: Pulmonary Hypertension: WHO Classification

- **Group 1:** PAH (pulmonary arterial hypertension)
- **Group 2:** PH due to left heart disease
- **Group 3:** PH due to lung disease and/or hypoxemia
- **Group 4:** CTEPH (chronic thromboembolic pulmonary hypertension)
- **Group 5:** PH due to unclear multifactorial mechanisms

### Appendix E: Pulmonary Hypertension: WHO/NYHA Functional Classes (FC)

<table>
<thead>
<tr>
<th>Treatment Approach*</th>
<th>FC</th>
<th>Status at Rest</th>
<th>Tolerance of Physical Activity (PA)</th>
<th>PA Limitations</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring for progression of PH and treatment of co-existing conditions</td>
<td>I</td>
<td>Comfortable at rest</td>
<td>No limitation</td>
<td>Ordinary PA does not cause undue dyspnea or fatigue, chest pain, or near syncope.</td>
<td></td>
</tr>
</tbody>
</table>

**Advanced treatment of PH with PH-targeted therapy - see Appendix F**

<table>
<thead>
<tr>
<th>Advanced treatment of PH with PH-targeted therapy - see Appendix F**</th>
<th>II</th>
<th>Comfortable at rest</th>
<th>Slight limitation</th>
<th>Ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>III</td>
<td>Comfortable at rest</td>
<td>Marked limitation</td>
<td>Less than ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>Dyspnea or fatigue may be present at rest</td>
<td>Inability to carry out any PA without symptoms</td>
<td>Discomfort is increased by any PA.</td>
<td>Signs of right heart failure</td>
</tr>
</tbody>
</table>

*PH supportive measures may include diuretics, oxygen therapy, anticoagulation, digoxin, exercise, pneumococcal vaccination. **Advanced treatment options also include calcium channel blockers.
### Appendix F: Pulmonary Hypertension: Targeted Therapies

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Drug Class</th>
<th>Drug Subclass</th>
<th>Drug</th>
<th>Brand/Generic Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of pulmonary arterial pressure through vasodilation</td>
<td>Prostacyclin* pathway agonist</td>
<td>Prostacyclin</td>
<td>Epoprostenol</td>
<td>Veletri (IV), Flolan (IV), Flolan generic (IV)</td>
</tr>
<tr>
<td></td>
<td>*Member of the prostanoid class of fatty acid derivatives.</td>
<td>Synthetic prostacyclin analog</td>
<td>Treprostinil</td>
<td>Orenitram (oral tablet), Remodulin (IV), Tyvaso (inhalation)</td>
</tr>
<tr>
<td></td>
<td>Endothelin receptor antagonist (ETRA)</td>
<td>Selective receptor antagonist</td>
<td>Ambrisentan</td>
<td>Letairis (oral tablet)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonselective dual action receptor antagonist</td>
<td>Bosentan</td>
<td>Tracleer (oral tablet)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Macitentan</td>
<td>Opsumit (oral tablet)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitric oxide-cyclic guanosine monophosphate enhancer</td>
<td>Phosphodiesterase type 5 (PDE5) inhibitor</td>
<td>Sildenafil</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tadalafil</td>
<td>Adcirca (oral tablet)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Guanylate cyclase stimulant (sGC)</td>
<td>Riociguat</td>
</tr>
</tbody>
</table>

#### V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol (Flolan)</td>
<td>2 ng/kg/min IV, increased by 1-2 ng/kg/min at intervals of at least 15 minutes</td>
<td>Based on clinical response</td>
</tr>
<tr>
<td>Epoprostenol (Veletri)</td>
<td>2 ng/kg/min IV, increased by 2 ng/kg/min every 15 minutes or longer</td>
<td>Based on clinical response</td>
</tr>
</tbody>
</table>

#### VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epoprostenol (Flolan)</td>
<td>Vial with powder for reconstitution: 0.5 mg, 1.5 mg</td>
</tr>
<tr>
<td>Epoprostenol (Veletri)</td>
<td>Vial: 0.5 mg/10 mL, 1.5 mg/10 mL</td>
</tr>
</tbody>
</table>
VII. References


Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1325</td>
<td>Injection, epoprostenol, 0.5 mg</td>
</tr>
</tbody>
</table>
Clinical Policy
Epoprostenol

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>02.17</td>
<td>03.17</td>
</tr>
<tr>
<td>11.21.17</td>
<td>02.18</td>
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<tr>
<td>11.20.18</td>
<td>02.19</td>
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<tr>
<td>03.15.19</td>
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<td>11.26.19</td>
<td>02.20</td>
</tr>
<tr>
<td>10.12.20</td>
<td>02.21</td>
</tr>
</tbody>
</table>

FC II is added to the prostanoid class of PH drugs. Safety criteria were removed unless they 1) represent contraindications or black box warnings not covered by a REMS program, and 2) provide specific lab/imaging parameters that must be met prior to initiation of therapy. An efficacy statement is added to the continuation criteria. Initial and continuation durations increased to 6 and 12 months respectively. Appendices covering PH group, functional class and therapy reorganized.

1Q18 annual review: Policies combined for commercial and Medicaid; No significant changes from previous corporate approved policy; Medicaid: removed WHO/NYHA classifications from initial criteria since specialist is involved in care; References reviewed and updated.

1Q 2019 annual review: no significant changes; references reviewed and updated.

Added HIM line of business due to addition of agent(s) to the HIM formulary with PA

1Q 2020 annual review: no significant changes; added statement that treatment plan detailing dose, quantity, and frequency; references reviewed and updated.

1Q 2021 annual review: no significant changes; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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