**Clinical Policy: Selexipag (Uptravi)**
Reference Number: CP.PHAR.196
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**
Selexipag (Uptravi®) is a prostacyclin receptor agonist.

**FDA Approved Indication(s)**
Uptravi is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) 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%), and PAH associated with congenital heart disease with repaired shunts (10%).

**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 Uptravi is medically 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. Dose does not exceed 3,200 mcg per day *(if request is for titration, provider must submit a titration plan)*.

   **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 NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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. If request is for a dose increase, new dose does not exceed 3,200 mcg per day (if request is for titration, provider must submit a titration plan).

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>
</tbody>
</table>
### CLINICAL POLICY
### Selexipag

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<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>
<tr>
<td>amlodipine (Norvasc®)</td>
<td>20 to 30 mg PO QD</td>
<td>30 mg/day</td>
</tr>
</tbody>
</table>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

### Appendix C: Contraindication/Boxed Warnings
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>
<tr>
<td>Advanced treatment of PH with PH-targeted therapy - see Appendix F**</td>
<td>II</td>
<td>Comfortable at rest</td>
<td>Slight limitation</td>
<td>Ordinary PA causes undue dyspnea or fatigue, chest pain, or near syncope.</td>
<td></td>
</tr>
<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>*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>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Iloprost</td>
<td>Ventavis (inhalation)</td>
</tr>
<tr>
<td></td>
<td>Non-prostanoid prostacyclin receptor (IP receptor) agonist</td>
<td>Selexipag</td>
<td>Uptravi (oral tablet)</td>
<td></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>Nitric oxide-cyclic guanosine monophosphate enhancer</td>
<td>Phosphodiesterase type 5 (PDE5) inhibitor</td>
<td>Sildenafil</td>
<td>Revatio (IV, oral tablet, oral suspension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tadalafil</td>
<td>Adcirca (oral tablet)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Guanylate cyclase stimulant (sGC)</td>
<td>Riociguat</td>
<td>Adempas (oral tablet)</td>
</tr>
</tbody>
</table>

### V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAH</td>
<td>200 mcg PO BID, increased at weekly intervals to highest tolerated dose up to 1,600 mcg BID</td>
<td>3,200 mcg/day</td>
</tr>
</tbody>
</table>

### VI. Product Availability

Tablets: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1,000 mcg, 1,200 mcg, 1,400 mcg, 1,600 mcg

### VII. References


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age restriction removed. FC II added to the prostanoid class of PH drugs.</td>
<td>02.17</td>
<td>03.17</td>
</tr>
<tr>
<td>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 groups, functional class and therapies reorganized.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1Q18 annual review: Policies combined for commercial, HIM 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.</td>
<td>11.20.17</td>
<td>02.18</td>
</tr>
<tr>
<td>1Q 2019 annual review: no significant changes; references reviewed and updated.</td>
<td>11.20.18</td>
<td>02.19</td>
</tr>
<tr>
<td>1Q 2020 annual review: no significant changes; added statement that titration plan be submitted; added HIM line of business; references reviewed and updated.</td>
<td>11.26.19</td>
<td>02.20</td>
</tr>
</tbody>
</table>
Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.12.20</td>
<td>02.21</td>
</tr>
</tbody>
</table>

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.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.
This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**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.