Clinical Policy: Sildenafil (Revatio)
Reference Number: CP.PHAR.197
Effective Date: 03.16
Last Review Date: 02.19
Line of Business: Commercial, HIM*, Medicaid

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

Description
Sildenafil (Revatio®) is a phosphodiesterase-5 inhibitor.

*For Health Insurance Marketplace (HIM), if request is through the pharmacy benefit, sildenafil (Revatio) oral suspension is non-formulary and cannot be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.

FDA Approved Indication(s)
Revatio is indicated for the treatment of pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1) in adults to improve exercise ability and delay clinical worsening. The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy.

Studies establishing effectiveness were short-term (12 to 16 weeks), and included predominately patients with New York Heart Association (NYHA) Functional Class II-III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (25%).

Limitation(s) of use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.

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 Revatio 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 60 mg per day (oral formulations) or 30 mg per day (intravenous formulations) in divided doses.
Approval duration:
Medicaid – 6 months
HIM – 6 months for oral tablets and IV solution (refer to HIM.PA.103 for oral suspension)
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.PHAR.21 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 60 mg per day (oral formulations) or 30 mg per day (intravenous formulations) in divided doses.

Approval duration:
Medicaid – 12 months
HIM – 12 months for oral tablets and IV solution (refer to HIM.PA.103 for oral suspension)
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.PHAR.21 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.PHAR.21 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>
<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: Contraindications/Boxed Warnings
- Contraindication(s):
  - Use with organic nitrates or riociguat
  - History of hypersensitivity reaction to sildenafil or any component of the tablet, injection, or oral suspension
- 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</td>
<td>I</td>
<td>Comfortable at</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>progression of PH and</td>
<td></td>
<td>rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>treatment of co-</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>existing conditions</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Advanced</td>
<td>II</td>
<td>Comfortable at</td>
<td>Slight limitation</td>
<td>Ordinary PA causes undue dyspnea or</td>
<td></td>
</tr>
<tr>
<td>treatment of PH</td>
<td></td>
<td>rest</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### CLINICAL POLICY

**Sildenafil**

#### Treatment Approach*

<table>
<thead>
<tr>
<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>with PH-targeted therapy - see Appendix F**</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>III</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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>Non-prostanoid prostacyclin receptor (IP receptor) agonist</td>
<td>Selexipag</td>
<td>Uptravi (oral tablet)</td>
<td></td>
</tr>
<tr>
<td>Endothelin receptor antagonist (ETRA)</td>
<td>Selective receptor antagonist</td>
<td>Ambrisentan</td>
<td>Letairis (oral tablet)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nonselective dual action receptor antagonist</td>
<td>Bosentan</td>
<td>Tracleer (oral tablet)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macitentan</td>
<td>Opsumit (oral tablet)</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tadalafil</td>
<td>Adcirca (oral tablet)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Guanylate cyclase stimulant (sGC)</td>
<td>Riociguat</td>
<td>Adempas (oral tablet)</td>
<td></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>Tablet and oral suspension: 5 mg or 20 mg PO TID, 4-6 hours apart Injection: 2.5 mg or 10 mg TID as an IV bolus</td>
<td>Tablet/oral suspension: 60 mg/day Injection: 30 mg/day</td>
</tr>
</tbody>
</table>

VI. Product Availability

- Tablets: 20 mg
- Oral suspension: 10 mg/mL
- Vial for injection: 10 mg/12.5 mL

VII. References


Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>02.16</td>
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</tr>
<tr>
<td>02.17</td>
<td>03.17</td>
</tr>
</tbody>
</table>

Policy split from CP.PHAR.33.PAH and converted to new template.
Criteria: added specialist requirement; removed echocardiogram as an option for confirming a PH diagnosis; removed hard stop after 3 months of therapy.
Appendices removed: 1) examples of calcium channel blocker contraindications; 2) nitrate therapy examples; 3) PAH definition.
FC II added to the prostanoid class of PH drugs. Safety criteria were removed unless they 1) represent contraindications or black
Reviews, Revisions, and Approvals

<table>
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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>1Q18 annual review: Policies combined for commercial, HIM and Medicaid; No significant changes from previous corporate approved policy; Medicaid/HIM: removed WHO/NYHA classifications from initial criteria since specialist is involved in care; References reviewed and updated.</td>
<td>11.20.17 02.18</td>
</tr>
<tr>
<td>1Q 2019 annual review: added disclaimer of NF status for oral solution formulation for HIM; references reviewed and updated.</td>
<td>11.20.18 02.19</td>
</tr>
</tbody>
</table>

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.
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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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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