Clinical Policy: Pretomanid
Reference Number: ERX.NPA.131
Effective Date: 03.01.20
Last Review Date: 02.20
Line of Business: Commercial, Medicaid

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

Description
Pretomanid is a nitroimidazooxazine antimycobacterial drug

FDA Approved Indication(s)
Pretomanid is indicated as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR), treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients.

Limitation(s) of use:
• Pretomanid tablets are not indicated for patients with:
  o Drug-sensitive (DS) tuberculosis
  o Latent infection due to Mycobacterium tuberculosis
  o Extra-pulmonary infection due to Mycobacterium tuberculosis
  o MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy
• Safety and effectiveness of pretomanid tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that pretomanid is medically necessary when the following criteria are met:

I. Initial Approval Criteria
A. Multi-Drug Resistant Tuberculosis (must meet all):
  1. Diagnosis of pulmonary MDR-TB or XDR-TB;
  2. Prescribed by or in consultation with an infectious disease specialist or a pulmonologist;
  3. Age ≥ 17 years;
  4. Prescribed in combination with Sirturo® (bedaquiline) and linezolid;
     *Prior authorization may be required for Sirturo and linezolid.
  5. Documented resistance to fluoroquinolones, unless contraindicated or clinically significant adverse effects are experienced;
  6. Dose does not exceed 200 mg (1 tablet) per day.
     Approval duration: 6 months

B. Other diagnoses/indications
  1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).
II. Continued Therapy
A. Multi-Drug Resistant Tuberculosis (must meet all):
   1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
   2. Member is responding positively to therapy;
   3. Member meets one of the following (a or b):
      a. Member continues to receive Sirturo and linezolid in combination with pretomanid;
      b. Member continues to receive Sirturo and has completed at least 4 weeks of linezolid therapy;
   4. If request is for a dose increase, new dose does not exceed 200 mg (1 tablet) per day.
   Approval duration: Up to a total treatment duration of 6 months (9 months if evidence of delayed culture conversion)

B. Other diagnoses/indications (must meet 1 or 2):
   1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
   2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information
   Appendix A: Abbreviation/Acronym Key
   FDA: Food and Drug Administration
   TI/NR: treatment-intolerant or nonresponsive
   MDR-TB: multi-drug resistant tuberculosis
   XDR-TB: extensively drug resistant tuberculosis

   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>pyrazinamide</td>
<td>Follow weight-based dosing in prescribing information</td>
<td>4,000 mg/dose</td>
</tr>
<tr>
<td>cycloserine</td>
<td>10 to 15 mg/kg PO QD or BID</td>
<td>1,000 mg/day</td>
</tr>
<tr>
<td>ethionamide</td>
<td>10 to 20 mg/kg PO QD or BID</td>
<td>1,000 mg/day</td>
</tr>
<tr>
<td>streptomycin</td>
<td>15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly</td>
<td>20 mg/kg/day</td>
</tr>
<tr>
<td>amikacin/kanamycin</td>
<td>15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly</td>
<td>15 mg/kg/day</td>
</tr>
<tr>
<td>capreomycin</td>
<td>15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly</td>
<td>1,000 mg/day</td>
</tr>
<tr>
<td>para-amino salicylic acid</td>
<td>8 to 12 g PO BID to TID</td>
<td>12 g/day</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500 to 1,000 mg PO or IV QD</td>
<td>1,000 mg/day</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400 mg PO or IV QD</td>
<td>400 mg/day</td>
</tr>
<tr>
<td>linezolid (Zyvox®)</td>
<td>1,200 mg PO QD</td>
<td>1,200 mg/day</td>
</tr>
<tr>
<td>Sirturo® (bedaquiline)</td>
<td>400 mg PO QD for the first 2 weeks, followed by 200 mg PO three times per week for remaining 24 weeks.</td>
<td>400 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): patients who have contraindications to Sirturo and/or linezolid
Boxed warning(s): none reported

Appendix D: General Information

- Pretomanid should only be used in combination with Sirturo and linezolid.
- Dosing of the combination regimen of pretomanid, bedaquiline, and linezolid can be extended beyond 26 weeks if necessary, to a maximum of 9 months, in patients with delayed culture conversion.
  - Delayed culture conversion: two consecutive negative sputum cultures following an initial positive culture.
- Laboratory confirmation of multi-drug resistant TB must show TB with an isolate showing genotypic or phenotypic resistance to isoniazid and rifampin.
- Laboratory confirmation of extensively drug resistant TB must show TB with an isolate showing genotypic or phenotypic resistance to isoniazid, rifampin, fluoroquinolones, as well as second-line injectable agents such as aminoglycosides or capreomycin.
- Linezolid starting dose of 1,200 mg daily for 26 weeks may be managed as follows:
  - Adjusted to 600 mg daily and further reduced to 300 mg daily as necessary for adverse reactions of myelosuppression, peripheral neuropathy, and optic neuropathy.
  - Doses of the regimen missed for safety reasons can be made up at the end of treatment; doses of linezolid alone missed due to adverse reactions should not be made up.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
</table>
| MDR-TB, XDR-TB | Administer in combination with bedaquiline and linezolid in a directly observed therapy (DOT) setting.  
  - Pretomanid: 200 mg PO QD for 26 weeks.  
  - Sirturo: 400 mg PO QD for 2 weeks followed by 200 mg 3 times per week (at least 48 hours between doses) for the remaining 24 weeks.  
  - Linezolid: 1,200 mg PO QD for 26 weeks.  
  
Patients may continue treatment with Sirturo and pretomanid without linezolid if the patient has previously received a total daily dose of linezolid 1,200 mg for at least 4 weeks. | 200 mg/day |

VI. Product Availability

Tablets: 200 mg

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>Policy created</td>
<td>09.24.19</td>
<td>02.20</td>
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**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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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