Clinical Policy: Pretomanid

Reference Number: CP.PMN.222
Effective Date: 03.01.20
Last Review Date: 02.20
Line of Business: Commercial, HIM, Medicaid Revision Log

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:
  - Drug-sensitive (DS) tuberculosis
  - Latent infection due to *Mycobacterium tuberculosis*
  - Extra-pulmonary infection due to *Mycobacterium tuberculosis*
  - 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.

It is the policy of health plans affiliated with Centene Corporation® 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 expert in the treatment of tuberculosis;
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 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. Multi-Drug Resistant Tuberculosis (must meet all)**:**

1. Currently receiving medication via Centene benefit 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 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
FDA: Food and Drug Administration
MDR-TB: multi-drug resistant tuberculosis
TI/NR: treatment-intolerant or nonresponsive
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 for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
pyrazinamide	Follow weight-based dosing in prescribing information	4,000 mg/dose
cycloserine	10 to 15 mg/kg PO QD or BID	1,000 mg/day
ethionamide	10 to 20 mg/kg PO QD or BID	1,000 mg/day
streptomycin	15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly	20 mg/kg/day
amikacin/kanamycin	15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly	15 mg/kg/day
capreomycin	15 mg/kg IM or IV QD or 25 mg/kg PO 3 times weekly	1,000 mg/day
para-amino salicylic acid	8 to 12 g PO BID to TID	12 g/day
levofloxacin	500 to 1,000 mg PO or IV QD	1,000 mg/day
Moxifloxacin	400 mg PO or IV QD	400 mg/day
linezolid (Zyvox®)	1,200 mg PO QD	1,200 mg/day
Sirturo® (bedaquiline)	400 mg PO QD for the first 2 weeks, followed by 200 mg PO three times per week for remaining 24 weeks.	400 mg/day

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
- CDC Centers of Excellence for TB: https://www.cdc.gov/tb/education/tb_coe/default.htm
- Pretomanid should only be used in combination with Sirturo and linezolid.
- Dosing of the combination regimen of pretomanid, Sirturo, 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; does of linezolid alone missed due to adverse reactions should not be made up.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
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

1. Pretomanid Prescribing Information. Hyderabad, India: Mylan; August 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf. Accessed September 6, 2019.
2. ClinicalTrials.gov [Internet]. Identifier: NCT02333799, A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis https://clinicaltrials.gov/ct2/show/NCT02333799. Accessed September 6, 2019
3. Talwar A, Tsang CA, Price SF, et al. Tuberculosis — United States, 2018. MMWR Morb Mortal Wkly Rep 2019;68:257–262. DOI: http://dx.doi.org/10.15585/mmwr.mm6811a2. Accessed September 6, 2019.
4. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO. Available at: https://apps.who.int/iris/bitstream/handle/10665/311389/9789241550529-eng.pdf
5. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Licence: CC BY-NC-SA 3.0 IGO. Available at: https://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1
6. FDA Briefing Document for Pretomanid tablet, 200mg. Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC): New York, NY: June 6, 2019. Available at: https://www.fda.gov/media/127592/download. Accessed September 6, 2019.
7. Pretomanid: Sponsor Briefing Document Antimicrobial Drugs Advisory Committee. New York, NY: June 6, 2019. Available at: https://www.fda.gov/media/127593/download. Accessed September 6, 2019.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	09.24.19	02.20

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.

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.