Clinical Policy: Pretomanid

Reference Number: PA.CP.PMN.222
Effective Date: 01/2020
Last Review Date: 01/2024

Revision Log

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 PA Health & Wellness® 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 (e.g., state or county public health department, specialists affiliated with TB Centers of Excellence as designated by the CDC, infectious disease specialists managing TB clinics);
3. Age ≥ 15 years;
4. Prescribed in combination with Sirturo® (bedaquiline) and linezolid;
   **Prior authorization may be required for Sirturo and linezolid.*
5. One of the following (a or b):
   a. Prescribed in combination with moxifloxacin (off-label);
   b. 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: 26 weeks

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Multi-Drug Resistant Tuberculosis (must meet all)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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 treatment beyond 26 weeks, provider attestation of delayed treatment response within the first 8 weeks as assessed by time to culture conversion, persistent culture positivity, clinical response to treatment, and other underlying clinical factors, or modified based on adverse events;

Approval duration: up to a total treatment duration of 26 weeks (9 months if evidence of delayed culture conversion)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   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): PA.CP.PMN.53

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 – PA.CP.PMN.53

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BPaL: bedaquiline, pretomanid, and linezolid
CDC: Centers for Disease Control
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®)	600 - 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 (total duration of 26 weeks*). • Linezolid: 600 mg PO QD for 26 weeks*. Patients 17 years of age or older 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. ** Treatment with the BPaL regimen can be extended beyond 26 weeks up to 9 months (39 weeks) based on delayed treatment response within the first 8 weeks as assessed by time to culture conversion, persistent culture positivity, clinical response to treatment, and other underlying clinical factors, or modified based on adverse events*	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 October 20, 2023.
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. Available at: https://clinicaltrials.gov/ct2/show/NCT02333799. Accessed October 30, 2023.
3. Talwar A, Tsang CA, Price SF, et al. Tuberculosis — United States, 2018. MMWR Morb Mortal Wkly Rep 2019;68(11):257–262. DOI: http://dx.doi.org/10.15585/mmwr.mm6811a2. Accessed October 30, 2023.
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. Accessed October 30, 2023.
5. WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment - Drug-Resistant Tuberculosis Treatment. 15 June 2020. Available at: https://www.who.int/publications/i/item/9789240007048. Accessed October 30, 2023.
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 October 30, 2023.
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 October 30, 2023.
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9. Provisional CDC Guidance for the Use of Pretomanid as part of a Regimen [Bedaquiline, Pretomanid, and Linezolid (BPaL)] to Treat Drug-Resistant Tuberculosis Disease. Updated May 4, 2023. Available at: https://www.cdc.gov/tb/topic/drtb/bpal/. Accessed October 30, 2023.
10. WHO-Rapid communication: Key changes to the treatment of drug-resistant tuberculosis. May 2022. Available at: https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2. Accessed October 30, 2023.
11. Center for Disease Control and Prevention. Drug-resistant TB. Updated October 13, 2022. Available at: https://www.cdc.gov/tb/topic/drtb/default.htm. Accessed October 30, 2023.
12. WHO consolidated guidelines on tuberculosis: module 5: management of tuberculosis in children and adolescents. 18 March 2022. Available at: https://www.who.int/publications/i/item/9789240046764. Accessed October 30, 2023.

Reviews, Revisions, and Approvals	Date
Policy created	01/2020
1Q 2021 annual review: no significant changes; references reviewed and updated.	01/2021
Clarified expert in the treatment of tuberculosis to include state or county public health department, specialists affiliated with any of the four TB Centers of Excellence as designated by the CDC, or ID specialists managing TB clinics.	04/2021
1Q 2022 annual review: references reviewed and updated.	01/2022
1Q 2023 annual review: lowered age requirement from 17 to 15 years per updated WHO 2022 guidance, clarified approval duration from 6 months to 26 weeks; for continued therapy reinforced therapy duration requirements that were previously only referenced in the approval duration; added alternative option if there is no documented fluoroquinolone resistance for off-label use when prescribed in combination with moxifloxacin; references reviewed and updated.	01/2023

Reviews, Revisions, and Approvals	Date
1Q 2024 annual review: updated linezolid dosing from 1,200 mg to 600 mg per updated CDC recommendations; references reviewed and updated.	01/2024