

Pretomanid

National Drug Monograph

October 2021

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information¹

Description/Mechanism of Action/Basic Spectrum of Activity

- Pretomanid is a novel systemic nitroimidazooxazine antibiotic approved for treatment of certain kinds of drug-resistant tuberculosis (TB). Primarily works by preventing TB cell wall synthesis

Indication(s) Under Review in This Document

- FDA approved under the limited population pathway (LPAD) in August of 2019 for
 - Pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) TB as part of a combination regimen with bedaquiline and linezolid (BPaL), in adults
- Pretomanid is NOT indicated in patients with drug sensitive pulmonary TB, extra-pulmonary TB or MDR TB that is NOT treatment-intolerance or nonresponsive to standard therapy, or for latent TB infections

Dosage Form(s) Under Review and Dosing Considerations

- 200 mg immediate-release tablet
- For treatment of XDR or treatment intolerant or non-responsive MDR TB, the recommended dosing is as follows
 - 200 mg of pretomanid daily for 26 weeks, in combination with bedaquiline (400mg daily for 2 weeks, then 200mg 3 times per week for 24 weeks) and linezolid (1200mg daily orally for 26 weeks, with dose adjustments for known linezolid toxicities)
 - The regimen should be taken with food
- Pretomanid MUST only be used with bedaquiline and linezolid, and the LPAD indication notes that approval is for that specific combination regimen
- Dosing can be extended beyond 26 weeks if necessary
- Prior to treatment, baseline labs should be completed, including AST/ALT, alkaline phosphatase, bilirubin, complete blood cell count (CBC), serum potassium, calcium, and magnesium (correct if abnormal) as well as an ECG
- If bedaquiline or pretomanid must be discontinued, the entire regimen must be discontinued.
- If linezolid is permanently discontinued in the first 4 weeks, the entire regimen should be discontinued, however if linezolid is discontinued beyond the 4th week, pretomanid and bedaquiline should be continued

Clinical Evidence Summary

Efficacy Considerations

- **In vitro data:**¹
 - Relevant spectrum of activity: *Mycobacterium tuberculosis* complex, with MIC 0.06-1 mcg/mL
 - Frequency of development of resistance in vitro ranged from 10⁻⁷ to 10⁻⁵ at 2 to 6 times the pretomanid MIC

- Mechanisms of resistance:
 - 5 *M. tuberculosis* genes are assoc with pretomanid resistance: *ddn*, *fgd1*, *fbiA*, *fbiB*, and *fbiC*¹
 - It is likely there are other mechanisms of resistance as some isolates with elevated MICs to pretomanid do not have these mutations
- **Clinical data:**^{1,2}
 - All baseline isolates tested in Clinical study 1 had a pretomanid MIC of 1 mcg/mL or lower
 - 2 out of 109 total patients relapsed, both with relapse TB isolate still susceptible to pretomanid
- Not approved for drug-sensitive tuberculosis, latent infection due to *M. tuberculosis*, extrapulmonary infection due to *M. tuberculosis*, MDR-TB that is not treatment-intolerant or nonresponsive to standard therapy
- The labeling additionally states that the safety and efficacy of pretomanid tablets have not been established in combination with drugs other than bedaquiline and linezolid
 - There is some early support for its use in various other combinations with bedaquiline, moxifloxacin, and pyrazinamide, but further evidence is needed
- **XDR-TB** is defined as TB with resistance to isoniazid, rifampin, any fluoroquinolone, and at least one injectable drug (amikacin, capreomycin, or kanamycin)
- **Nonresponsive MDR-TB** is defined as TB with resistance to isoniazid and rifampin that does not respond to treatment or for which treatment is discontinued because of side effects
- The FDA approval of pretomanid in combination with bedaquiline and linezolid was based primarily on one clinical trial. Efficacy data are summarized in **Table 1**. In addition, data from the ZeNix trial evaluating different doses of linezolid in the BPAL regimen are available in abstract form only.⁵

Table 1: Efficacy results from clinical trials^{1,2}

| Study and Design | Intervention, Inclusion/Exclusion, and Outcomes | Population | Results |
|--|--|---|--|
| <p>Conradie et al. (2020)²</p> <p>Open-label, single-group study with ongoing follow up at three sites in South Africa</p> | <p>Dosing regimens</p> <ul style="list-style-type: none"> ● Pretomanid: 200 mg daily for 26 weeks ● Bedaquiline: 400 mg once daily for 2 weeks, then 200 mg three times weekly for 24 weeks ● Linezolid: 1200 mg once daily for up to 26 weeks, with dose adjustment based on toxicity. (Note: dosing was changed from 600 mg twice daily to 1200 mg daily mid-study to evaluate for reduced toxicity) ● Treatment was 26 weeks (could be extended to 39 weeks if cultures were positive at week 16) ● Early discontinuation or modification of the regimen was allowed per judgment of the data safety and monitoring committee <p>Comparator None</p> <p>Inclusion</p> <ul style="list-style-type: none"> ● At least 14 years old ● MDR- or XDR-TB on culture or via molecular testing in past 3 months ● Drug resistant TB documented by phenotypic or genotypic testing ● For MDR-TB, not responsive to treatment for 6 months OR inability to continue second-line regimen due to side effects | <p>N = 109</p> <ul style="list-style-type: none"> ● 44 on linezolid 600 mg twice daily ● 65 on linezolid 1200 mg daily ● 2 had treatment extended for additional 3 months <p>Patient demographics</p> <ul style="list-style-type: none"> ● Median age 35 years ● 52% male ● 76% black ● Median BMI 19.7 ● 51% HIV-positive (on antiretrovirals) <p>TB demographics</p> <ul style="list-style-type: none"> ● 84% with cavities on chest Xray ● 16 without positive baseline cultures ● 65% XDR ● 17% MDR nonresponsive ● 17% MDR stopped for ADE ● All but 3 isolates ≤WHO critical MIC to bedaquiline (1 µg/mL) | <p>Primary outcome (unfavorable outcome at 6 months post-treatment)</p> <ul style="list-style-type: none"> ● 11 patients (10%) <ul style="list-style-type: none"> ○ 7 deaths ○ 1 withdrew consent ○ 2 relapses ○ 1 lost to follow-up ● 90% favorable outcome <p>Subgroup analyses</p> <ul style="list-style-type: none"> ● XDR: 89% favorable outcome |

| | | | |
|---|--|--|--|
| | <ul style="list-style-type: none"> HIV-positive patients allowed if CD4+ cell count >50 cells/mm³ and they were on antiretroviral therapy <p>Exclusion</p> <ul style="list-style-type: none"> Grade 3 or 4 baseline peripheral neuropathy <p>Primary outcome</p> <ul style="list-style-type: none"> Unfavorable outcome: Composite of bacteriologic failure, clinical failure, or disease relapse | <ul style="list-style-type: none"> All isolates ≤ WHO critical MIC to linezolid (1 µg/mL) All MIC ≤1 µg/mL pretomanid <p>Prior therapy</p> <ul style="list-style-type: none"> Time since diagnosis 12 months 100 patients had received TB medications in the month prior Most common drugs: fluoroquinolones, pyrazinamide, terizidone, clofazimine, para-aminosalicylic acid, ethambutol, ethionamide | <ul style="list-style-type: none"> MDR: 92% favorable outcome Not affected by HIV status or linezolid dose |
| <p>Conradie et al. (2021)⁵</p> <p>ZeNix trial:</p> <p>Phase 3, partially blinded RCT studied varying doses of linezolid as part of the BPaL regimen</p> | <p>Regimens: Pretomanid and bedaquiline dosed as above Patients randomized 1:1:1:1 to</p> <ul style="list-style-type: none"> Linezolid 1200mg daily x 6 months Linezolid 1200mg daily x 2months Linezolid 600mg daily x 6 months Linezolid 600mg daily x 2 months <p>Inclusion:</p> <ol style="list-style-type: none"> XDR-TB* Pre-XDR-TB** MDR-TB and documented non-response x 6 mo. MDR-TB: and unable to continue second line drug regimen due to intolerance to PAS, ethionamide, aminoglycosides or fluoroquinolones <p>Exclusion: TB likely to be resistant to any BPaL components Prolonged QT, heart failure Pregnancy Grade 3 or 4 peripheral neuropathy Hemoglobin < 9 g/dL Platelets < 100 x 10⁹/L AST or ALT > 3 X ULN Bilirubin > 1.5 X ULN Serum creatinine > 1.5 x ULN Albumin < 3 g/dL HIV with viral load > 1000 copies/mL or CD4+<100 cells/uL</p> <p>Primary outcome: resolution of clinical disease and bacteriologic success after 6 months</p> | <p>Demographics:</p> <p>Very limited data as only in abstract form from IAS meeting</p> <p>Linezolid 1200mg QD x 6 mo. (n=45) Linezolid 1200mg QD x 2 mo. (n=46) Linezolid 600mg QD x 6 mo. (n=45) Linezolid 600mg QD x 2 mo. (n=45)</p> <p>mean age of all was 37 years 67.4% were men 63.5% were White 19.9% were HIV positive</p> <p>41% were XDR-TB 47% MDR-TB with resistance to quinolone or injectable 6% MDR-TB with failure to respond 5% MDR-TB unable to tolerate first line drugs</p> | <p>Efficacy: Clinical success</p> <p>93% for those receiving 1200 mg for 6 mo.</p> <p>88% for those receiving 1200 mg for 2 mo.</p> <p>90% for those receiving 600 mg for 6 mo.</p> <p>84% for those receiving 600 mg for 2 mo.</p> |

*XDR-TB: documented culture/molecular test + (for MTB) and documented resistance to rifamycins, a fluoroquinolone AND an injectable (may be sensitive or resistant to isoniazid). ** Pre-XDR-TB: documented culture/ molecular test + (for MTB) with resistance to rifamycins, and a fluoroquinolone OR an (may be sensitive or resistant to isoniazid)

Efficacy data summary: In XDR-TB and complicated MDR-TB, a combination regimen of bedaquiline, linezolid, and pretomanid for 26 weeks achieved 90% treatment success at 6 months after completion of therapy. This success rate is similar to that of standard of care regimen rifampin, pyrazinamide, isoniazid, and ethambutol in drug-sensitive TB. This is

especially notable given that these results were found in TB cases that are often difficult to treat. A reduced dose and/or duration of linezolid does not seem to have a major impact on efficacy.

Safety Considerations

Safety Results from Clinical Trials:

- Safety analysis from the FDA approval study is summarized below in **Table 2**. Note that adverse events are reported for the combination regimen of bedaquiline, linezolid, and pretomanid, and NOT pretomanid alone.

Table 2: Safety results from clinical trials

| Study | Adverse events | Comments |
|--|---|---|
| <p>Conradie et al. (2020)²</p> <p>FDA approval study</p> <p>N = 109</p> <p>All received pretomanid, bedaquiline and linezolid for 6 months (could be extended to 9 months)</p> | <p>Overall</p> <ul style="list-style-type: none"> • 109 had at least 1 adverse event (100%) • 19 had serious adverse events (17%) • 62 had adverse events Grade 3 or higher that occurred or worsened during treatment (57%) <p>Adverse effects occurring in at least 10% of patients</p> <ul style="list-style-type: none"> • Peripheral neuropathy 81% - most occurred after 8 weeks of therapy and required dose reduction or discontinuation of linezolid. Severe neuropathy occurred in 22% of cases • Acne 39% • Anemia 37% • Nausea 37%, Vomiting 34%, dyspepsia 24%, abdominal pain 19%, decreased appetite 22%, abnormal weight loss 10%, diarrhea 10% • Musculoskeletal pain 29% • Headache 28% • Increase in transaminases 28% • Increased gamma-glutamyl transferase 17% • Rash 21%, Pruritis 20% • Pleuritic pain 19% • Lower respiratory tract infection 15% • Hyperamylasemia 14% • Hemoptysis 13% • Cough 12% • Visual impairment 12% - 2 patients developed severe optic neuritis necessitating discontinuation of linezolid. Both resolved. • Hypoglycemia 11% | <ul style="list-style-type: none"> • Side effects are for bedaquiline, linezolid, and pretomanid combination regimen • Authors attribute peripheral neuropathy and myelosuppression to linezolid as these are known linezolid toxicities • It was noted that similar tolerability was seen with 1200mg daily or 600mg twice daily of linezolid • It was noted that despite a high rate of elevated transaminases, other than 1 patient who died from pneumonia, all others were able to complete treatment |
| <p>Conradie et al. (2021)⁵</p> <p>ZeNix trial: Phase 3, RCT, varying dose/duration of linezolid</p> | <p>Myelosuppression and peripheral neuropathy were more common with higher doses and longer duration of linezolid</p> <p>Anemia: 22% (1200mgx 6 mo.), 17% (1200mg x 2 mo.), 2% (600mgx 6 mo.) and 7% (600mgx 2 mo.)</p> <p>Peripheral neuropathy: 38%, 24%, 24% and 13%, respectively and 4 cases of optic neuropathy all in the 1200mgx26wk arm, that reversed</p> | <ul style="list-style-type: none"> • More patients on 1200mg x 6 months required dose modification |

- **Boxed warnings:** None
- **Contraindications:** Combination therapy with bedaquiline and linezolid is contraindicated when bedaquiline and linezolid are contraindicated
- **Other warnings / precautions:**

- **Adverse reactions**
 - **Common:** Peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased transaminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea
- **Serious Adverse Events / Deaths / Discontinuation:**
 - 6 patients died in the FDA approval study during treatment
 - None had the regimen permanently discontinued and all completed at least 26 weeks of therapy

Serious Adverse Events and Monitoring

Monitoring for potentially serious adverse events, such as hepatotoxicity, myelosuppression, peripheral and optic neuropathy, and QT prolongation is recommended

- **Hepatic:**
 - **AST/ALT, alkaline phosphatase and bilirubin should be done at baseline, 2 weeks, and at least monthly during therapy**
 - The regimen should be interrupted if AST/ALT elevations are accompanied by total bilirubin greater than 2 times the upper limit of normal (ULN), AST/ALT are > 8 times the ULN or > 5 times the ULN and sustained for at least 2 weeks
 - Patients should avoid alcohol and other hepatotoxins and educated on signs and symptoms of hepatic injury
- **Complete blood count:** (anemia, thrombocytopenia and leukopenia)
 - **CBC should be done at baseline, 2 weeks and at least monthly during therapy**
 - Recent data from the ZeNix trial showed that lower doses or shorter durations of linezolid along with bedaquiline and pretomanid is associated with reduced myelotoxicity and peripheral neuropathy with similar efficacy as with higher doses.⁵
 - Linezolid should be interrupted or dose reduced if patients develop or have worsening myelosuppression
- **Peripheral and optic neuropathy**
 - **Visual function should be monitored in all patients, and if changes in vision occur, linezolid should be stopped and ophthalmologic consultation should be sought**
 - Peripheral neuropathy is a known adverse event with prolonged linezolid and is generally reversible or improved with appropriate monitoring, dose adjustment or interruption
- **QT Prolongation**
 - **QT prolongation is a known adverse event with bedaquiline. An ECG should be done at baseline and at least 2, 12 and 24 weeks after starting treatment.**
 - The entire regimen should be discontinued if serious ventricular arrhythmias occur or the QTcF is > 500 msec, confirmed by a second ECG
 - Several factors, including electrolyte disturbances can increase the likelihood of QT prolongation and should be obtained at baseline and corrected if abnormal.
- **Drug-drug interactions: Strong inducers of CYP3A have been shown to decrease the C_{max} and AUC of pretomanid**
 - Co-administration with rifampin for 7 days decreased pretomanid AUC by 66%
 - Co-administration with efavirenz for 7 days decreased pretomanid AUC by 35%
 - While not studied formally, in vitro data suggest pretomanid inhibits OAT3, potentially leading to an increase in OAT3 substrates (e.g. methotrexate) and patients should be monitored closely for increased adverse events of the substrate with dose adjustments as appropriate
- **Reproductive effects**
 - Pretomanid caused testicular atrophy and impaired fertility in rats. Patients should be advised of this information and that data is not available in humans
- **Lactic acidosis**
 - Lactic acidosis has been reported with BPaL and is a known side effect of linezolid

- Patients who develop recurrent nausea and vomiting should receive immediate evaluation, including bicarbonate and lactic acid levels and interruption of therapy should be considered

Pharmacokinetics / Pharmacodynamics¹

- Absorption increased with a high fat, high calorie meal
- Metabolized through multiple pathways with none dominant, approximately 20% metabolized by CYP3A4
- 53% excreted in the urine; 1% unchanged, 38% excreted in the feces
- Effect of renal and hepatic impairment on pretomanid is unknown

Other Therapeutic Options

Alternative treatments for XDR-TB and nonresponsive MDR-TB is often highly individualized and should include a combination of drugs. The ATS 2019 Clinical guidelines on drug-resistant TB suggest at least 5 drugs in the intensive phase of treatment and 4 drugs in the continuation phase for MDR-TB and that the intensive phase regimen last between 5 to 7 months after culture conversion and the total treatment duration of 15-21 months after culture conversion. Treatment duration for XDR-TB is suggested to be between 15-24 months after culture conversion.

- **XDR-TB** is defined as TB with resistance to isoniazid, rifampin, any fluoroquinolone, and at least one injectable drug (amikacin, capreomycin, or kanamycin)
- **Nonresponsive MDR-TB** is defined as TB with resistance to isoniazid and rifampin that does not respond to treatment or for which treatment is discontinued because of side effects

In terms of specific agents to be considered for inclusion, a later-generation fluoroquinolone and bedaquiline are recommended. Linezolid, clofazimine, and cycloserine are suggested, as well as amikacin or streptomycin when susceptibility of these drugs is confirmed.

Projected Place in Therapy

- *Mycobacterium tuberculosis* infection can be a serious condition that requires long treatment courses with a combination of limited drug options. When isolates are resistant to preferred options, such as in XDR-TB and MDR-TB, drug options are further limited.
- The World Health Organization guidelines from 2020 on the treatment of MDR-TB suggest BPaL may be used under operational research conditions in MDR-TB that is resistant to fluoroquinolones, who have had either no more than 2 weeks prior exposure to bedaquiline or linezolid. They suggest BPaL may be considered in individuals for whom the design of an effective regimen based on existing WHO recommendations is not possible. While high clinical success rates were noted in MDR and XDR-TB, the high rate of adverse events was concerning to the WHO, particularly those related to linezolid
- Guidelines from the American Thoracic Society were completed in 2019 prior to the approval of pretomanid and its use was not considered in their recommendations.
- Pretomanid is a new antituberculosis drug FDA-approved for the treatment of XDR and non-responsive or treatment-intolerant-MDR pulmonary tuberculosis in combination with bedaquiline and linezolid under the **FDA limited population for antimicrobial drugs pathway, created to streamline approval of drugs for serious or life-threatening infections with an unmet medical need**. As a limitation of use, pretomanid is not indicated for
 - **Drug-susceptible TB**
 - **Latent infection due to TB**
 - **Extra-pulmonary TB**
 - **MDR-TB that is not treatment-intolerant or non-responsive**

- **Safety and efficacy data has not been examined except as part of the BPaL regimen and pretomanid must only be used in combination with those medications as part of the recommended dosing regimen. Administration should be through directly observed therapy (DOT).**
- Clinical evidence to support this combination is limited to one ongoing trial (Nix-TB) and the linezolid dose adjustment trial (Ze-Nix).
- Due to very limited data, at this time, pretomanid should only be used in patient for whom other better-studied and guideline-recommended antituberculosis drugs are not an option due to drug resistance or intolerance. If clinical trial benefit can be confirmed, the BPaL regimen may be able to offer a shorter, more cost-effective and highly effective regimen for MDR and XDR-TB, and with the lower doses may have a more favorable tolerability profile. Additional study is required before using this regimen in place of guideline-recommended regimens for MDR-TB.

References

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