PDL DRUG REVIEW

Proprietary Name: Pretomanid®
Common Name: pretomanid
PDL Category: Antimycobacterial/Anti-Tuberculosis

Comparable Products	Preferred Drug List Status
Sirturo	Non-Preferred

Summary

Pharmacology/Usage: Pretomanid® is an oral nitro-imidazooxazine antimycobacterial drug that kills actively replicating *M. tuberculosis* by inhibiting mycolic acid biosynthesis, thus blocking cell wall production.

Indications: Limited Population: As part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR) or treatment-intolerant or non-responsive multidrug-resistant (MDR) tuberculosis (TB). Approval of this indication is based in limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients.

Limitations of use: Pretomanid® tablets are not indicated in patients with the following conditions: Drug-sensitive (DS) TB, 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.

The safety and effectiveness of Pretomanid® tablets have not been established for its use in combination with other drugs other than bedaquiline and linezolid as part of the recommended dosing regimen.

There is no pregnancy category for this product; however, the risk summary indicates that there are no studies or available data on use in pregnant women to inform any drug-associated risks. There are risks associated with active TB during pregnancy. There are clinical considerations, as active TB in pregnancy is associated with adverse maternal and neonatal outcomes, including maternal anemia, caesarean delivery, preterm birth, low birth weight, and perinatal infant death. The safety and efficacy of use in the pediatric population have not been established.

Dosage Forms: Tablets: 200mg

Recommended Dosage: Use only in combination with bedaquiline and linezolid as part of the recommended dosing regimen. Emphasize the need for compliance with the full course of therapy to patients. Administer the combination regimen by directly observed therapy (DOT).

Prior to starting the combination regimen, assess for symptoms and signs of liver disease (such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, and hepatomegaly). Obtain laboratory tests, including ALT, AST, alkaline phosphatase, and bilirubin. Obtain complete blood count. Obtain serum potassium, calcium, and magnesium and correct if abnormal. Obtain an ECG before initiation of treatment.

Take Pretomanid® 200mg PO once daily for 26 weeks. Swallow whole with water. Take bedaquiline 400mg PO QD for 2 weeks followed by 200mg 3 times per week, with at least 48 hours between doses, for 24 weeks for a total of 26 weeks. Take linezolid starting at 1200mg QD for 26 weeks, with dose adjustments to 600mg QD and further reduction to 300mg QD or interruption of dosing as needed for known linezolid adverse reactions of

myelosuppression, peripheral neuropathy, and optic neuropathy. Take the combination regimen with food. Dosing of the combination regimen can be extended beyond 26 weeks, if necessary.

If either bedaquiline or Pretomanid® tablets are discontinued, the entire combination regimen should also be discontinued.

Drug Interactions: Co-administration of Pretomanid® with rifampin and efavirenz resulted in a decrease in Pretomanid® plasma levels. Avoid co-administration of the combination regimen with rifampin, efavirenz or other strong or moderate CYP3A4 inducers.

If Pretomanid® is co-administered with OAT3 substrate drugs (e.g. methotrexate), monitor for OAT3 substrate drug-related adverse reactions and consider dosage reduction for OAT3 substrate drugs, if needed.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Pretomanid® tablets, bedaquiline and linezolid combination regimen). There was no placebo data to compare with in the prescribing information.* The most frequently reported adverse events included peripheral neuropathy (81%), acne (39%), anemia (37%), nausea (37%), vomiting (34%), musculoskeletal pain (29%), headache (28%), transaminases increased (28%), dyspepsia (24%), decreased appetite (22%), rash (21%), pruritus (20%), abdominal pain (19%), pleuritic pain (19%), gamma-glutamyltransferase increased (17%), lower respiratory tract infection (15%), hyperamylasemia (14%), hemoptysis (13%), cough (12%), visual impairment (12%), hypoglycemia (11%), abnormal loss of weight (10%), diarrhea (10%), constipation (8%), gastritis (8%), neutropenia (8%), dry skin (7%), hypertension (7%), electrocardiogram QT prolonged (6%), hyperlipasemia (6%), insomnia (6%), and thrombocytopenia (6%).

Laboratory abnormalities include ALT >3 and ≤5 x ULN (6%), ALT >5 and ≤8 x ULN (5%), AST >3 and ≤5 x ULN (6%), AST >5 and ≤8 x ULN (2%), total bilirubin >1 x ULN and ≤2 x ULN (6%), total bilirubin >2 x ULN (2%), hemoglobin ≤7.9mg/dl (6%), neutrophils absolute count ≤749/mm^3 (5%), platelets ≤49,999/mm^3 (2%), and lipase >2 x ULN (5%).

Hepatic adverse reactions were reported with the combination regimen of Pretomanid® tablets, bedaquiline, and linezolid. Avoid alcohol and hepatotoxic agents, including herbal supplements and drugs other than bedaquiline and linezolid while on Pretomanid® tablets, especially in patients with impaired hepatic function. Monitor signs and symptoms and laboratory tests at a minimum at baseline, at two weeks, and then monthly while on treatment and as needed. If evidence of new or worsening liver dysfunction occurs, test for viral hepatitides and discontinue other hepatotoxic medications.

Myelosuppression (including anemia, leukopenia, thrombocytopenia) was reported with the combination regimen. Complete blood counts should be monitored at a minimum at baseline, at two weeks, and then monthly.

Peripheral neuropathy and optic neuropathy were reported with the combination regimen. Neuropathy associated with linezolid is generally reversible or improved with appropriate monitoring and interruption, dose reduction, or discontinuation of linezolid dosing. Monitor visual function in all patient receiving the combination regimen.

QT prolongation was reported with the combination regimen. Obtain an ECG before the start of treatment, and at least 2, 12, and 24 weeks after starting treatment with the combination regimen. Obtain serum potassium, calcium, and magnesium at baseline and correct if abnormal. Discontinue the regimen if the patient develops clinically significant ventricular arrhythmia or a QTcF interval of >500ms, confirmed by repeat ECG.

Lactic acidosis was reported with the combination regimen. Patients who develop recurrent nausea or vomiting should receive immediate medical evaluation, including evaluation of bicarbonate and lactic acid levels.

Contraindications: Pretomanid® tablets used in the combination regimen are contraindicated in patients for whom bedaquiline and/or linezolid are contraindicated. Refer to the prescribing information for each individual product.

Manufacturer: Mylan Specialty

Analysis: The safety and efficacy of Pretomanid® were assessed in an open-label study conducted in 3 centers in South Africa in patients with XDR, treatment-intolerant MDR, or non-responsive MDR pulmonary TB, including 51% of the patients who were HIV-positive. The patients received a combination regimen for 6 months (extended to 9 months in 2 patients) with 24 months of follow-up. Treatment failure was defined as the incidence of bacteriologic failure (reinfection; culture conversion to positive status with different *M. tuberculosis* strain), bacteriologic relapse (culture conversion to positive status with same *M. tuberculosis* strain), or clinical failure through follow-up until 6 months after the end of treatment.

Results suggested that of the 107 patients assessed, outcomes were classified as success for 95 patients (89%) and failure for 12 patients (11%). The success rate significantly exceeded the historical success rate for XDR-TB based on a literature review. The outcomes were similar in both HIV negative and HIV positive patients. Results can be seen in the table below, which was adapted from the prescribing information. Note that TI is treatment intolerant and NR is nonresponsive.

Outcome		Total	XDR-TB	TI/NR MDR-TB
	Total assessable	107	71	36
Success	Success (culture negative status at 6 months post treatment)	95 (89%)	63 (89%)	32 (89%)
Failure	Death	7	6	1
	Relapse post treatment	2	1	1
	Withdrawal, loss to follow-up, or contaminated cultures	3	1	2
	Total Failure	12 (11%)	8 (11%)	4 (11%)

Place in Therapy: Pretomanid® is indicated, as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR) or 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. The safety and efficacy 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. In an open-label study, the treatment success rate was 89%, having a negative culture status at 6 months post treatment.

It is recommended that Pretomanid® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Pretomanid [package insert]. Morgantown, WV: Mylan Specialty; 2019.